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(54) Title: SUBSTITUTED PIPERIDINES AS MODULATORS OF THE MELANOCORTIN RECEPTOR

(57) Abstract: Selected substituted piperidine compounds are effective for prophylaxis and treatment of diseases, such as obesity and the like. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving activation of the melanocortin receptor. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

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SUBSTITUTED PIPERIDINES AS MODULATORS OF THE MELANOCORTIN RECEPTOR

FIELD OF THE INVENTION

5

The present invention relates generally to the fields of medicinal chemistry and, more specifically, to novel compounds and their use as anti-obesity agents.

10

BACKGROUND OF THE INVENTION

Obesity, defined as an excess of body fat relative to lean body mass, contributes to and complicates other diseases. For example, obesity substantially increases the 15 risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary artery disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, as well as cancers of the endometrium, breast, prostate and colon. As a major cause of preventable death 20 in the United States today, obesity poses a major public health challenge.

Overweight is defined today as a body mass index (BMI) of 25-29.9 kg/m², and obesity is defined as a BMI^{>30} kg/m². Over 60% of the adult population of the United States and 25 Australia are either overweight (BMI of 25-29.9 kg/m²) or obese (BMI>30kg/m²). More than 20% of adults fall into this latter category.

The cause of obesity is quite complex and not merely the result of voluntary overeating. Rather, the differential 30 body composition observed between obese and normal subjects results from differences in both metabolism and neurologic/metabolic interactions.

The purpose of weight loss and weight maintenance is to reduce health risks. If weight is regained, health risks 35 increase. A majority of patients who lose weight regain it, so the challenge to the patient and the practitioner is to maintain weight loss. Because of the tendency to regain

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weight after weight loss, the use of long-term medication to aid in the treatment of obesity may be indicated for carefully selected patients.

The drugs used to promote weight loss are

5 traditionally anorexiants or appetite suppressants. Three classes of anorexiant drugs have been developed, all of which affect neurotransmitters in the brain. They may be designated as follows: (1) those that affect catecholamines, such as dopamine and norepinephrine; (2) those that affect 10 serotonin; and (3) those that affect more than one neurotransmitter. These drugs work by increasing the secretion of dopamine, norepinephrine, or serotonin into the synaptic neural cleft, by inhibiting the reuptake of these neurotransmitters into the neuron, or by a combination of 15 both mechanisms. Sibutramine inhibits the reuptake of norepinephrine and serotonin. Orlistat is not an appetite suppressant and has a different mechanism of action; it blocks about one-third of fat absorption.

Weight loss drugs approved by the FDA for long-term 20 use may be useful as an adjunct to diet and physical activity for patients with a BMI>27 who also have concomitant obesity-related risk factors or diseases. Our thinking about drug therapy has undergone radical changes over the past few years.

25 Of recent interest as a target has been the melanocortin receptor family. The term melanocortin ("MC") defines a family of peptide hormones that regulate diverse physiological functions through transmembrane G-protein coupled receptors. Melanocortins include melanocyte-stimulating hormones (MSH) such as α -MSH, β -MSH and γ -MSH, as well as adrenocorticotropic hormone (ACTH). The melanocortin (MC) receptors ("MCRs") are a group of cell surface proteins that mediate a variety of physiological effects, including adrenal gland function, production of

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cortisol and aldosterone, control of melanocyte growth and pigment production, thermoregulation, immunomodulation and analgesia. In the past several years, five distinct melanocortin receptor subtypes have been identified. The 5 five MC receptors, termed MCR1, MCR2, MCR3, MCR4 and MCR5, all couple in a stimulatory fashion to cAMP. MCR1, MCR3, MCR4 and MCR5 constitute subtypes of MSH receptors. The MCRs stimulate adenyl cyclase to generate cAMP.

The MC1 receptor is present on melanocytes and 10 melanoma and is involved in skin pigmentation. The MCR2 receptor is the ACTH receptor and is present predominantly in the adrenal gland. MCR2 plays a role in adrenal steroidogenesis. The mRNA for the MCR3 receptor has been found in the brain, as well as in placental and gut tissues. 15 The MCR4 receptor has been found primarily in the brain. The MCR5 receptor is expressed in the brain, as well as in several peripheral tissues and has been implicated in exocrine gland function.

The melanocortin peptides also mediate a number of 20 other physiological effects. They are reported to affect motivation, learning, memory, behavior, inflammation, body temperature, pain perception, blood pressure, heart rate, vascular tone, natriuresis, brain blood flow, nerve growth and repair, placental development, aldosterone synthesis and 25 release, thyroxin release, spermatogenesis, ovarian weight, prolactin and FSH secretion, uterine bleeding in women, sebum and pheromone secretion, sexual activity, penile erection, blood glucose levels, intrauterine fetal growth, food motivated behavior, as well as other events related to 30 parturition.

Recently, MC receptor MCR4 has been shown to function in the regulation of body weight and food intake. Early studies on mice that expressed agouti ectopically, which is a MCR4 antagonist, produced obese animals. Subsequent work

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has shown that MCR3 and MCR4 antagonists stimulated food intake and that MCR4 knockout mice are obese. Synthetic MC4 agonist peptides that mimic melanocortins and bind to MCR4 injected into the brain, cause suppression of feeding in 5 normal and mutant obese mice. Targeted disruption of MCR4 causes mice to develop a maturity onset of obesity associated with hyperphagia, hyperinsulinemia and hyperglycemia (Huszar et al., *supra*). Stimulation of the MC4 receptor by an endogenous ligand, α -MSH, produces a 10 satiety signal and may be the downstream mediator of the leptin signalling pathway. These results indicate that the brain MC receptor MCR-4 functions in regulating food intake and body weight and is a promising target in the treatment of obesity. It is believed that by providing potent MC-4 15 receptor agonists, appetite may be suppressed and weight loss benefits may be achieved. See J. Wikberg, *Eur. J. Pharm.*, 375, 295-310 (1999).

Melanotan II (MTII) is an α -MSH peptide superagonist for MCR4. (M. Hadley et al., *Discovery and Development of 20 Novel Melanogenic Drugs, Integration of Pharmaceutical Discovery and Development: Case Studies*, Borchardt et al., ed., Plenum Press, New York 1998). Other cyclic and linear α -MSH peptides also have been studied. See, for example, C. Haskell-Luevano et al., *J. Med. Chem.*, 40, 2133-39 (1997); 25 H. Schiöth et al., *Brit. J. Pharmacol.*, 124, 75-82 (1998); H. Schiöth et al., *Eur. J. Pharmacol.*, 349, 359-66 (1998); M. Hadley et al., *Pigment Cell Res.*, 9, 213-34 (1996); M. Bednarek et al., *Peptides*, 20, 401-09 (1999); and U.S. Patent Nos. 6,054,556, 6,051,555 and 5,576,290.

30 WO98/11128, published 19 March 1998, describes phenylalanine derivatives.

WO00/78317, published 28 December 2000, describes piperidine derivatives as integrin receptor antagonists. EP1086947, published 29 August 2000, describes piperidine

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compounds as agonists and antagonists for the SST receptor. WO00/35874, published 22 June 2000, describes arylpiperidine compounds as intermediates for the preparation of 5HT1A agonists and antagonists. WO00/35875, published 22 June 5 2000, describes arylpiperidine compounds as intermediates for the preparation of 5HT1A agonists and antagonists. WO00/25786, published 11 May 2000, describes substituted piperidines as potassium channel inhibitors. United States Patent No. 5,518,735, issued May 21, 1996, describes 10 phenylalanine derivatives which prevent coagulation or thrombosis. WO97/19908, published 5 June 1997, describes phenylalanine derivatives as fungicides. WO97/49673, published 31 December 1997, describes phenylalanine derivatives as thrombin inhibitors.

15 WO95/34311, published 21 December 1995, describes substituted piperazine compounds as growth hormone releasing agents. US Patent No. 5,681,954, issued Oct. 28, 1997, describes substituted piperazines as inhibitors of calmodulin. WO97/03060, published 30 January 1997,

20 describes piperazine derivatives as cysteine protease inhibitors. US Patent No. 6,057,290, issued May 2, 2000, describes piperazine derivatives as cysteine protease inhibitors. WO97/19919, published 5 June 1997, describes sulfonamides as having anti-thrombin activity. US Patent No.

25 5,244,895, issued Sept. 14, 1993, describes piperazine derivatives as antiulcer agents. EP 513691, published 31 July 1996, describes piperazine derivatives as antiulcer agents. US Patent No. 5,244,895, issued Sept. 14, 1993, describes sulfonamides having smooth muscle relaxation

30 activity. WO94/05693, published 17 March 1994, describes piperazinyl-phenylalanine derivatives as tachyquinine antagonists. J. Sturzebecher et al. J. Enzyme Inhib., 9, 87-99 (1995), describes piperazinyl-phenylalanine derivatives as thrombin inhibitors. M. Böhm et al. J. Med.

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Chem., 42, 458-77 (1999), describes piperazinyl-phenylalanine derivatives as thrombin inhibitors. J. Sturzebecher et al., J. Med. Chem., 40, 3091-99 (1997), describes piperazinyl-phenylalanine derivatives as thrombin inhibitors. H. Sakamoto, et al. Pept. Chem., 27, 375-8 (1989) describes piperazinyl-phenylalanine derivatives as chymotrypsin inhibitors. H. Sakamoto, et al., Bull. Chem. Soc. Jpn., 64, 2519-23 (1991) describes piperazinyl-phenylalanine derivatives as chymotrypsin inhibitors. G. Wagner, et al., Pharmazie, 36, 597-603 (1981), describes piperazinyl-phenylalanine derivatives as serine protease inhibitors. E.J. Jacobsen et al. J. Med. Chem., 42, 1525-36 (1999) describes thiazolyl ureas as stromelysin inhibitors. WO97/40031, published 30 October 1997, describes thiazolyl ureas as metalloprotease inhibitors.

WO01/10842, published 15 February 2001, describes melanocortin receptor binding compounds. WO99/64002, published 16 December 1999, describes spiroperidines as melanocortin receptor agonists. WO00/74679, published 14 December 2000, describes piperidine compounds as melanocortin receptor agonists.

However, compounds of the current invention have not been described as inhibitors of MCRs such as for the treatment of obesity.

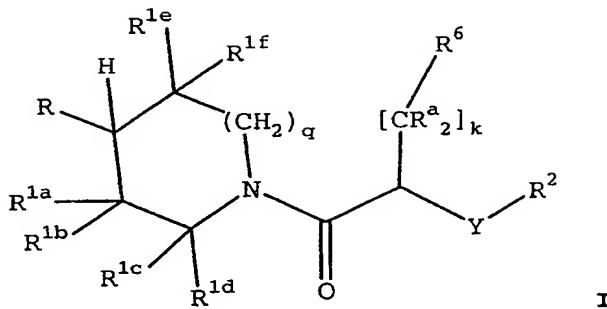
25

DESCRIPTION OF THE INVENTION

A class of compounds useful in treating obesity is defined by Formula I

30

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wherein Y is -NH-, -CH₂-, or -O-;

preferably -NH- or -CH₂-; and

5 more preferably -NH-;

wherein R is selected from

- a) alkyl,
- b) -(CH₂)_n-cycloalkyl,
- c) -(CH₂)_n-aryl, and
- 10 d) -(CH₂)_n-heterocyclyl;

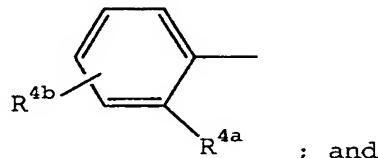
wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl group is optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl group is optionally substituted with 1 to 3 groups selected from R⁵;

15 preferably selected from

- a) -(CH₂)_n-C₃₋₈-cycloalkyl,
 - b) -aryl,
 - 20 c) unsubstituted benzyl, and
 - d) -(CH₂)_n-5-6-membered heterocyclyl;
- wherein R is substituted at the 2-position of the cycloalkyl, heterocyclyl, benzyl and aryl groups with a radical selected from R⁴; and wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 2 additional radicals selected from R⁴; and the heterocyclyl group is

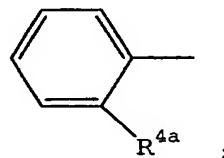
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optionally substituted with 1 to 2 additional
radicals selected from R⁴ and oxo;
more preferably R is phenyl ortho substituted
with a radical selected from R⁴ and optionally
5 substituted with a radical selected from R⁴;
even more preferably



; and

of particular importance



;

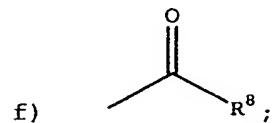
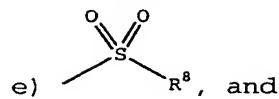
10 wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are independently
selected from R⁴; or wherein R^{1a} and R^{1b}, or R^{1d} and R^{1c}
form oxo; or wherein R^{1e} and R^{1c} form an alkylene or
alkenylene bridge; or wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d}
together with the piperazine ring forms an optionally
15 substituted 1,2,3,4-tetrahydro-quinoxaliny ring;
preferably wherein R^{1a-f} are independently selected from
R⁴; or wherein R^{1a} and R^{1b} or R^{1d} and R^{1c} form oxo; or
wherein R^{1e} and R^{1c} form an C₁₋₄-alkylene or C₂₋₄-
alkenylene bridge; or wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d}
20 together with the piperazine ring forms an optionally
substituted 1,2,3,4-tetrahydro-quinoxaliny ring; and
more preferably R^{1a-f} are independently selected from
R⁴; or wherein R^{1a} and R^{1b} or R^{1d} and R^{1c} form oxo;
even more preferably R^{1a-f} are H;

25 wherein R² is selected from

- a) alkyl,
- b) -(CH₂)_n-cycloalkyl,
- c) -(CH₂)_n-aryl;

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d) $-(\text{CH}_2)_n$ -heterocyclyl,



5 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl group is optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl group is optionally substituted with 1 to 3 groups selected from R⁵;

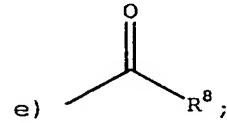
10 preferably selected from

a) $-(\text{CH}_2)_n$ -C₃₋₈-cycloalkyl,

b) $-(\text{CH}_2)_n$ -aryl,

c) $-(\text{CH}_2)_n$ -4-10-membered heterocyclyl,

15 d)



20 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; and the heterocyclyl group is optionally substituted with 1 to 3 groups selected from R⁴ and oxo;

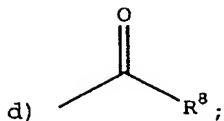
more preferably selected from

a) $-(\text{CH}_2)_n$ -C₃₋₆-cycloalkyl,

b) $-(\text{CH}_2)_n$ -phenyl,

25 c) $-(\text{CH}_2)_n$ -5-10-membered heterocyclyl, and

- 10 -



wherein the cycloalkyl and aryl groups are
optionally substituted with 1 to 3 radicals
selected from R⁴; and the heterocyclyl group is
optionally substituted with 1 to 3 radicals
selected from R⁴ and oxo;

even more preferably selected from

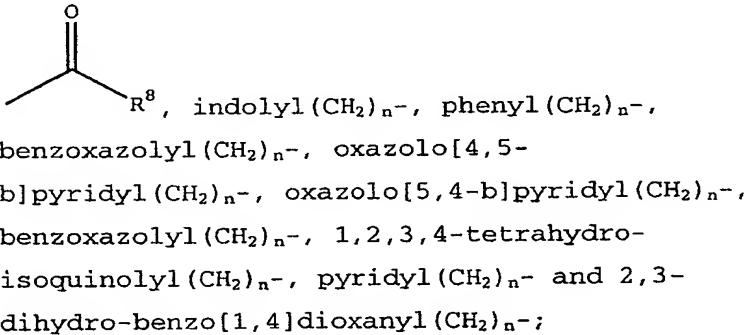
a) -(CH₂)_n-C₃₋₆-cycloalkyl,

b) -(CH₂)_n-phenyl, and

c) -(CH₂)_n-6-10-membered heterocyclyl;

wherein the cycloalkyl and aryl groups are
optionally substituted with 1 to 2 groups
selected from R^{4b}; and the heterocyclyl group
is optionally substituted with 1 to 2 groups
selected from R^{4b} and oxo; and

of particular importance selected from



wherein R² is optionally substituted with 1
to 2 groups selected from R^{4b};

wherein R³ is independently selected from H, halo, amino,
haloalkyl, alkyl, phenyl, haloalkoxy, and alkoxy; or R³
is an alkenylene bridge;

preferably H, halo, amino, C₁₋₆-haloalkyl, C₁₋₆-alkyl,
phenyl, C₁₋₆-haloalkoxy and C₁₋₆-alkoxy; or R³ is an C₂₋₄-
alkenylene bridge;

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more preferably H, chloro, bromo, iodo, phenyl,
fluoro, amino, C₁₋₂-alkyl, C₁₋₂-haloalkyl, C₁₋₂-
haloalkoxy and C₁₋₂-alkoxy;

even more preferably H, chloro, bromo, iodo,
5 fluoro, amino, methyl, methoxy,
 trifluoromethyl and trifluoromethoxy;
 and of particular interest are H, chloro,
 bromo, amino, methyl, trifluoromethyl and
 methoxy;

10 wherein R⁴ is selected from H, alkyl, -(CH₂)_n-cycloalkyl, -
 (CH₂)_n-aryl, -(CH₂)_n-heterocyclyl, halo, -(CH₂)_n-OR⁹, -
 NR⁹SO₂R⁷, -[C(R⁷)₂]_pNR⁹SO₂R⁷, -[C(R⁷)₂]_pNR⁹C(O)R⁷, -N(R⁹)₂, -
 C(O)NR⁹R⁹, -NR⁹C(O)R⁷, -NR⁹CO₂R⁷, cyano, -COOR⁹, -(CH₂)_n-
 C=OR⁷, -(CH₂)_n-C=SR⁷, -(CH₂)_n-C=(NR⁹)R⁷, -NR⁹C=(NR⁷)N(R⁹)₂, -
15 [C(R⁷)₂]_pN(R⁹)₂, nitro, -SO₂N(R⁹)₂, -S(O)_mR⁷, -C(R⁷)₂SO₂CF₃,
 hydroxyalkyl, haloalkyl and haloalkoxy;
 preferably H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-
 aryl, -(CH₂)_n-4-10-membered heterocyclyl, halo, -(CH₂)_n-
 OR⁹, -NR⁹SO₂R⁷, -N(R⁹)₂, -C(O)NR⁹R⁹, -NR⁹C(O)R⁷, -NR⁹CO₂R⁷,

20 nitro, cyano, -(CH₂)_n-C(O)R⁷, -C(O)OR⁹, -(CH₂)_n-C(S)R⁷, -
 (CH₂)_n-C=(NR⁹)R⁷, -NR⁹C=(NR⁷)N(R⁷)₂, -[C(R⁷)₂]_pNR⁹SO₂R⁷, -
 [C(R⁷)₂]_pNR⁹C(O)R⁷, -[C(R⁷)₂]_pN(R⁹)₂, -SO₂N(R⁹)₂, -S(O)_mR⁷,
 -C(R⁷)₂SO₂CF₃, C₁₋₆-hydroxyalkyl, C₁₋₆-haloalkyl and C₁₋₆-
 haloalkoxy; and

25 more preferably H, C₁₋₂-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl,
 -(CH₂)_n-phenyl, -(CH₂)_n-4-10-membered heterocyclyl,
 fluoro, chloro, -(CH₂)_n-OR^{9a}, -NR^{9a}SO₂R⁷, -NR^{9a}R^{9b}, -
 C(O)NR^{9a}R^{9b}, -NR^{9a}C(O)R⁷, cyano, nitro, -(CH₂)_n-
 C(O)R⁷, -C(O)OR^{9a}, -(CH₂)_n-C(S)R⁷, -(CH₂)_n-C=(NR^{9a})R⁷,
 -NR^{9a}C=(NR^{9a})N(R⁷)₂, -[C(R⁷)₂]_pNR^{9a}R^{9b}, -[CH₂]_pNR^{9a}SO₂R⁷,
 -[CH₂]_pNR^{9a}C(O)R⁷, -SO₂NR^{9a}R^{9b}, -S(O)_mR⁷, -C(R⁷)₂SO₂CF₃,
 C₁₋₂-hydroxyalkyl C₁₋₂-haloalkyl and C₁₋₂-haloalkoxy;

30 wherein R^{4a} is selected from -(CH₂)_n-OR^{9a}, -NR^{9a}SO₂R^{7a}, 4-6-
 membered heterocyclyl, -[CH₂]_pNR^{9a}SO₂R^{7a}, -NR^{9a}R^{9b}, -

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$C(O)NR^{9a}R^{9b}$, $-NR^{9b}C(O)R^{7a}$, $-[CH_2]_pNR^{9b}C(O)R^{7a}$, $-(CH_2)_n-C(O)R^{7a}$,
 nitro, $-C(O)OR^{9a}$, $-(CH_2)_n-C(S)R^{7a}$, $-[C(R^{7a})_2]_pNR^{9a}R^{9b}$, $-SO_2NR^{9a}R^{9b}$, $-S(O)_mR^{7a}$ and $-C(R^{7a})_2SO_2CF_3$;
 preferably 4-5-membered heterocyclyl, $-NR^{9a}SO_2R^{7a}$, $-NR^{9a}R^{9b}$,
 5 $-C(O)NR^{9a}R^{9b}$, $-C_{1-3}-NR^{9a}SO_2R^{7a}$, $-C_{1-3}-NR^{9a}C(O)R^{7b}$, $-NR^{9b}C(O)R^{7a}$
 and $-C_{1-3}-NR^{9a}R^{9b}$; and
 more preferably selected from $-C_{1-2}-alkyl-NR^{9a}SO_2R^{7a}$, $-NR^{9a}SO_2R^{7a}$, 4-5-membered heterocyclyl $-NR^{9a}R^{9b}$, $-C(O)NR^{9a}R^{9b}$, $-C_{1-2}-alkyl-NR^{9a}C(O)R^{7b}$, $-NR^{9b}C(O)R^{7a}$ and $-C_{1-2}-alkyl-NR^{9a}R^{9b}$;

10 wherein R^{4b} is selected from H, C_{1-2} -alkyl, $-(CH_2)_n-C_{5-6}-$
 cycloalkyl, $-(CH_2)_n$ -phenyl, $-(CH_2)_n$ -4-10-membered
 heterocyclyl, fluoro, chloro, $-OR^{9a}$, $-(CH_2)_n-OR^{9a}$, $-NR^{9a}SO_2R^{7a}$, $-NR^{9a}R^{9b}$, $-C(O)NR^{9a}R^{9b}$, $-NR^{9a}C(O)R^{7b}$, $-(CH_2)_n-$
 15 $C(O)R^{7a}$, nitro, $-C(O)OR^{9a}$, $-(CH_2)_n-C(S)R^{7a}$, $-[C(R^{7a})_2]_pNR^{9a}R^{9b}$,
 $-SO_2NR^{9a}R^{9b}$, $-S(O)_mR^{7a}$, $-C(R^{7a})_2SO_2CF_3$, cyano, C_{1-2} -haloalkyl
 and C_{1-2} -haloalkoxy; and
 preferably H, methyl, cyclopentyl, cyclohexylmethyl,
 phenyl, benzyl, $-(CH_2)_n$ -4-10-membered heterocyclyl,
 20 fluoro, chloro, $-OR^{9a}$, $-(CH_2)_n-OR^{9a}$, $-NR^{9a}SO_2R^{7a}$, $-NR^{9a}R^{9b}$,
 $-C(O)NR^{9a}R^{9b}$, $-NR^{9a}C(O)R^{7b}$, $-(CH_2)_n-C(O)R^{7a}$, $-C(O)OR^{9a}$, $-$
 $[C(R^{7a})_2]_pNR^{9a}R^{9b}$, $-SO_2NR^{9a}R^{9b}$, $-SO_2R^{7a}$, trifluoromethyl and
 trifluoromethoxy;

wherein R^5 is selected from halo, $-OR^9$, $NHSO_2R^7$, $-N(R^9)_2$,
 25 cyano, $-COR^7$, $-[C(R^7)_2]_nN(R^9)_2$, nitro, $-SO_2N(R^9)_2$, $-S(O)_mR^7$,
 haloalkyl, and haloalkoxy;
 preferably halo, $-OR^9$, $-NHSO_2R^7$, $-N(R^9)_2$, cyano, $-COR^7$, $-$
 $[C(R^7)_2]_nN(R^9)_2$, nitro, $-SO_2N(R^9)_2$, $-S(O)_mR^7$, $C_{1-6}-$
 haloalkyl and C_{1-6} -haloalkoxy;

30 more preferably halo, $-OR^{9a}$, $-NR^{9a}R^{9b}$, $-[C(R^7)_2]_nNR^{9a}R^{9b}$,
 and $-SO_2NR^{9a}R^{9b}$; and
 even more preferably chloro, fluoro, hydroxyl, $-$
 $NR^{7a}R^{7b}$ and $-SO_2N(R^7a)_2$;

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wherein R⁶ is selected from aryl and heteroaryl, wherein R⁶ is optionally substituted with one or more R³; preferably phenyl, naphthyl and 6-membered heteroaryl, wherein R⁶ is optionally substituted with one or more R³;

5 more preferably naphthyl or phenyl optionally substituted with one or two R³; and of particular interest phenyl optionally substituted with one or two R³;

10 wherein R⁷ is selected from H, alkyl, -(CH₂)_n-cycloalkyl, -(CH₂)_n-heterocyclyl, -(CH₂)_n-aryl, aminoalkyl, alkylamino, alkenyl, alkylcarbonylaminoalkyl, alkylthioalkyl, alkylaminoalkyl, alkoxyalkyl and alkoxy; preferably H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl, -(CH₂)_n-phenyl, amino-C₁₋₆-alkyl, C₁₋₆-alkylamino, C₂₋₆-alkenyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl and C₁₋₆-alkoxy; and

15 20 more preferably H, C₁₋₄-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl, -(CH₂)_n-phenyl, amino-C₁₋₄-alkyl, C₁₋₄-alkylamino, C₂₋₄-alkenyl, C₁₋₄-alkylthio-C₁₋₄-alkyl, C₁₋₄-alkylcarbonylamino-C₁₋₄-alkyl, C₁₋₄-alkylamino-C₁₋₄-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl and C₁₋₄-alkoxy;

25 25 wherein R^{7a} is selected from H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl; and preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

30 wherein R^{7b} is selected from amino-C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkylamino, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, H, C₁₋₃-alkyl,

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- (CH₂)_n-C₃₋₆-cycloalkyl, - (CH₂)_n-4-10-membered heterocyclyl and - (CH₂)_n-phenyl; and

5 preferably amino-C₁₋₃-alkyl, C₁₋₃-alkylamino, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₁₋₃-alkyl, H, C₁₋₃-alkyl, - (CH₂)_n-C₃₋₆-cycloalkyl, - (CH₂)_n-4-10-membered heterocyclyl and - (CH₂)_n-phenyl;

wherein R⁸ is selected from

- a) heterocyclyl,
- 10 b) aminoalkyl,
- c) aminoalkylamino,
- d) alkylaminoalkylamino,
- e) alkylaminoalkyl,
- f) arylaminoalkyl,
- 15 g) arylalkylaminoalkyl,
- h) heterocyclylalkylaminoalkyl,
- i) aryl,
- j) alkyl,
- k) aralkyl,
- 20 l) heterocyclylalkyl,
- m) cycloalkylalkyl,
- n) -OR⁹
- o) aminoalkoxy,
- p) N-(heterocyclylalkyl)amino,
- 25 q) aralkyl where the alkyl portion is substituted with amino, hydroxy or alkylamino, and
- r) heterocyclylalkylenyl where the alkylenyl portion is substituted with amino, hydroxy or alkylamino;
- wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl groups are optionally substituted with 1 to 3 groups selected from R⁵;
- 30

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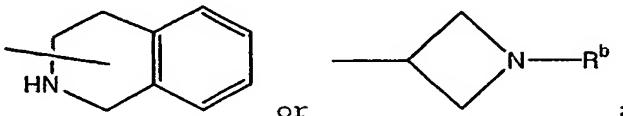
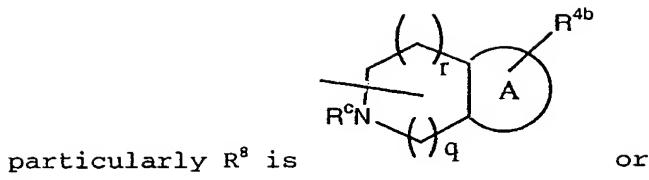
preferably selected from

- a) 4-10-membered heterocyclyl,
 - b) amino-C₁₋₆-alkyl,
 - c) amino-C₁₋₆-alkylamino,
 - 5 d) C₁₋₆-alkylamino-C₁₋₆-alkylamino,
 - e) C₁₋₆-alkylamino-C₁₋₆-alkyl,
 - f) arylamino-C₁₋₆-alkyl,
 - g) aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl,
 - h) 4-10-membered heterocyclyl-C₁₋₆-alkylamino-C₁₋₆-alkyl,
 - 10 i) aryl,
 - j) C₁₋₆-alkyl,
 - k) aryl-C₁₋₆-alkyl,
 - l) heterocyclyl-C₁₋₆-alkyl,
 - m) C₃₋₆-cycloalkyl-(CH₂)_n-,
 - 15 n) -OR⁹
 - o) amino-C₁₋₆-alkoxy,
 - p) N-(4-10-membered heterocyclyl-C₁₋₆-alkyl)amino,
 - q) aryl-C₁₋₆-alkyl where the alkyl portion is
substituted with amino, hydroxy or C₁₋₆-alkylamino,
 - 20 and
 - r) 4-10-membered heterocyclyl-C₁₋₆-alkylenyl where the
alkylenyl portion is substituted with amino,
hydroxy or C₁₋₆-alkylamino;
- more preferably selected from
- 25 a) amino-C₁₋₄-alkylamino,
 - b) amino-C₁₋₄-alkyl,
 - c) C₁₋₄-alkylamino-C₁₋₄-alkylamino,
 - d) C₁₋₄-alkylamino-C₁₋₄-alkyl,
 - e) phenyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
 - 30 f) phenylamino-C₁₋₄-alkyl,
 - g) 4-10-membered heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-
alkyl,
 - h) N-(4-10-membered heterocyclyl-C₁₋₄-alkyl)amino,
 - i) C₁₋₄-alkyl,

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- j) C_{3-6} -cycloalkyl-(CH_2) $_n$ -,
- k) aryl-(CH_2) $_n$ -,
- l) 4-10-membered heterocyclyl-(CH_2) $_n$ -,
- m) $R^{3a}O^-$,
- 5 n) amino-C₁₋₄-alkoxy,
- o) phenyl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₄-alkylamino, and
- p) 4-10-membered heterocyclyl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or C₁₋₄-alkylamino;
- 10 even more preferably selected from
 - a) amino amino-C₁₋₄-alkylamino,
 - b) amino-C₁₋₄-alkyl,
- 15 c) C₁₋₄-alkylamino-C₁₋₄-alkylamino,
- d) C₁₋₄-alkylamino-C₁₋₄-alkyl,
- e) phenylamino-C₁₋₄-alkyl,
- f) phenyl-C₁₋₂-alkylamino-C₁₋₄-alkyl,
- g) 4-10-membered heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
- 20 h) N-(4-10-membered heterocyclyl-C₁₋₄-alkyl)amino,
- i) C₁₋₄-alkyl,
- j) C_{3-6} -cycloalkyl-(CH_2) $_n$ -,
- k) aryl-(CH_2) $_n$ -,
- 25 l) 4-10-membered heterocyclyl-(CH_2) $_n$ -,
- m) amino-C₁₋₄-alkoxy,
- n) phenyl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₄-alkylamino, and
- 30 o) 4-10-membered heterocyclyl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino;

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5 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl groups are optionally substituted with 1 to 3 groups selected from R⁵;

10 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl groups are optionally substituted with 1 to 3 groups selected from R⁵;

15 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; and the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo;

20 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 2 groups selected from R^{4b}; and the heterocyclyl groups are optionally substituted with 1 to 2 groups selected from R^{4b} and oxo;

25 wherein R^{8a} is selected from

- a) 5-10-membered heterocyclyl,
- b) aryl, and

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c) benzyl;

wherein the aryl and heterocyclyl groups are optionally substituted with 1 to 3 radicals selected from C₁₋₆-alkyl, halo, hydroxyl, alkoxy, amino, alkylamino, cyano, -NHC(O)R⁷, -COR⁷, C₁₋₆-haloalkyl and C₁₋₆-haloalkoxy;

5 wherein R⁹ is selected from H, alkyl, alkenyl, cycloalkyl-(CH₂)_n-, heterocyclyl-(CH₂)_n-, aryl-(CH₂)_n-, aminoalkyl, alkylcarbonylaminoalkyl, cycloalkylaminoalkyl, 10 cycloalkylalkylaminoalkyl, heteroarylaminooalkyl, heteroarylalkylaminoalkyl, arylaminoalkyl, arylalkylaminoalkyl, heteroaryloxyalkyl, heteroarylalkyloxyalkyl, arylalkyloxyalkyl, aryloxyalkyl, alkylthioalkyl, alkylaminoalkyl, hydroxyalkyl and 15 alkoxyalkyl; preferably H, C₁₋₆-alkyl, alkenyl, C₃₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, aryl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkyl-C₁₋₆-20 alkylamino-C₁₋₆-alkyl, 5-6-membered heteroarylaminoo-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, arylamino-C₁₋₆-alkyl, aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 5-6-membered heteroaryloxy-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryloxy-C₁₋₆-alkyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, 25 C₁₋₆-alkylamino-C₁₋₆-alkyl, C₁₋₆-hydroxyalkyl and C₁₋₆-alkoxy-C₁₋₆-alkyl;

wherein R^{9a} is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n- and phenyl-(CH₂)_n-, and
30 preferably H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, and phenyl-(CH₂)_n-,

wherein R^{9b} is selected from H, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₃₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-,

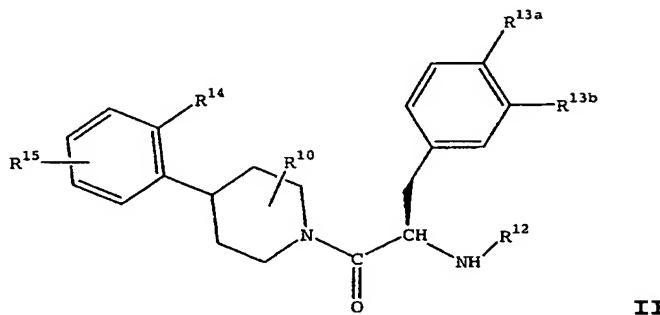
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phenyl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 5-6-membered heteroaryl-amino-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl,
5 phenylamino-C₁₋₆-alkyl, phenyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 5-6-membered heteroaryloxy-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, phenyl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, phenoxy-C₁₋₆-alkyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-alkyl, C₁₋₆-hydroxyalkyl and C₁₋₆-alkoxy-C₁₋₆-alkyl; and
10 preferably H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, phenyl-(CH₂)_n-, amino-C₁₋₃-alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroaryl-amino-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl, phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroaryloxy-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenoxy-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-hydroxyalkyl and C₁₋₃-alkoxy-C₁₋₃-alkyl;
15 wherein R^a are independently selected from H, and alkyl or the two R^a's together form cycloalkyl;
20 25 preferably H, and C₁₋₆-alkyl;
more preferably H or methyl; and
even more preferably R^a are H;
where R^b is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n- and phenyl-(CH₂)_n;
30 wherein R^c is H or methyl;
wherein A is selected from phenyl or 5-6-membered heteroaryl;
wherein k is 0 or 1; preferably 1;

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- wherein m is 0, 1 or 2; preferably 2;
 wherein n is 0, 1, 2, 3 or 4; preferably 0, 1, 2 or 3;
 wherein p is 1 or 2;
 wherein r is 0 or 1; and
 5 wherein q is 0 or 1.

The invention also relates to compounds of Formula II



10

- wherein R¹⁰ is selected from H, chloro or fluoro; or wherein
 R¹⁰ is a C₁₋₄-alkylene bridge;
 preferably H;
 wherein R¹² is selected from optionally substituted phenyl-
 15 C₁₋₂-alkylenyl, optionally substituted 5-10 membered

heteroaryl and ; provided the optionally substituted heterocyclyl is not nitro substituted;

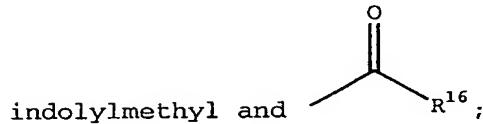
preferably , optionally substituted phenyl-C₁₋₃-alkyl, and optionally substituted 5-10-membered heterocyclyl;

20

more preferably oxazolylpyridyl, 4-(N,N-dimethylamino)phenylmethyl, 2,2-dimethyl-

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oxazolidinyl, benzodioxanyl methyl, pyridylmethyl,



indolylmethyl and

- wherein R^{13a} and R^{13b} are independently selected from H,
fluoro, iodo, bromo, chloro, C₁₋₂-alkyl, C₁₋₂-haloalkyl,
5 phenyl, and C₁₋₂-alkoxy; or wherein R^{13a} and R^{13b} together
form an C₁₋₄-alkenyl enyl bridge;
preferably R^{13a} is selected from H, bromo, chloro,
phenyl, trifluoromethyl and methoxy;
more preferably H and chloro;
- 10 preferably R^{13b} is H;
wherein R¹⁴ is selected from R¹⁹R²⁰N-, R¹⁹R²⁰N-C₁₋₄-alkyl,
(R²¹R²²N-) (O=)C-, C₁₋₄-haloalkyl, C₂₋₄-hydroxyalkyl,
heterocyclyloxy-C₁₋₄-alkyl, aryloxy-C₁₋₄-alkyl and C₁₋₄-
alkoxycarbonyl;
- 15 preferably trifluoromethyl, 2-hydroxyethyl, 1-
hydroxyethyl, R¹⁹R²⁰N-, R¹⁹R²⁰N-C₁₋₂-alkyl and (R²¹R²²N-
) (O=)C-;
more preferably N-pyrrolidinylcarbonyl, N-
morpholinocarbonyl, N-
- 20 piperidinylethylaminocarbonyl, benzylaminocarbonyl,
N-methyl-N-benzylaminocarbonyl,
aminoethylaminocarbonyl, pyridylaminocarbonyl,
methylthioethylaminocarbonyl,
methylcarbonylaminoethylaminocarbonyl, 1-
25 methylpyrrolidinylethylaminocarbonyl,
phenethylaminocarbonyl, phenylaminocarbonyl,
cyclohexylmethylaminocarbonyl, N-methyl-N-
phenethylaminocarbonyl, N,N-dimethylaminocarbonyl,
4-chlorophenylmethylaminocarbonyl,
30 phenoxyphenethylaminocarbonyl, allylaminocarbonyl,
4-methylpiperazinylcarbonyl, 4-
acetyl piperazinylcarbonyl, isopropylaminocarbonyl,

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1-(N-cyclopropylmethylamino)ethyl, 1-(N-methyl-N-methylcarbonylamino)ethyl, 1-(N-isopropylamino)ethyl, 1-(N-isobutyl-N-methylamino)ethyl, N-cyclopropylmethyl-N-propylaminomethyl, N,N-
5 dicyclopropylmethylaminomethyl, 1-(N-propyl-N-methylamino)ethyl, 1-(N-methyl-N-methysulfonylamino)ethyl, triazolylmethyl, imidazol-1-ylmethyl, 2-isopropylimidazol-1-yl-
10 methyl, 2-propylimidazol-1-yl-methyl, 2-oxo-pyrid-1-yl-methyl, 3-pyridyl-oxyethyl, 2-methylimidazol-1-yl-methyl, tetrazolylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, 2-oxo-pyrrolidin-1-yl-methyl, 2-oxo-piperidin-1-yl-methyl, 4,5-dihydro-2-oxo-oxazol-3-yl-methyl, pyrrolidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, piperazin-1-yl-methyl, 4-methylpiperazin-1-yl-methyl, piperidin-1-yl-methyl, 1-(N-ethyl-N-methylamino)ethyl, 1-(N,N-dipropylamino)ethyl, 1-(N,N-diisopropylamino)ethyl, 1-(N-(1-
15 ethoxycarbonyl)cycloprop-2-ylmethyl-N-methylamino)ethyl, 1-(N-(2-methylbutyl)-N-methylamino)ethyl, 1-(N-(4-methylcarbonylaminophenyl)methyl-N-methylamino)ethyl, 1-(N,N-dimethylamino)ethyl, 1-(N,N-dimethylaminomethyl, N-
20 cyclopropylmethyl-N-methysulfonylamino)ethyl, 1-(N-(3-thienyl)methyl-N-methylamino)ethyl, 1-(N-phenylmethoxyethyl-N-methylamino)ethyl, 1-(N-(2-methoxyphenyl)methyl-N-methylamino)ethyl, 1-(N-(4-pyridyl)methyl-N-methylamino)ethyl, 1-(N-(2-pyrrolidinyl)methyl-N-methylamino)ethyl, 1-(N-(3-methoxyphenyl)methyl-N-methylamino)ethyl, 1-(N-(4-methoxyphenyl)methyl-N-methylamino)ethyl, 1-(N-
25
30

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benzyl-N-methylamino)ethyl, 1-(N-methyl-N-
aminoethylamino)ethyl, 1-(N-cyclohexylmethyl-N-
methylamino)ethyl, N,N-dimethylaminomethyl, N-(1-
hydroxyethyl)-N-methylaminomethyl, N-(1-
5 hydroxyethyl)-N-methylaminomethyl, N-propyl-N-
methylsulfonylamino, N-(methylsulfonyl)-N-
propylamino, N-(methylsulfonyl)-N-
cyclopropylmethyleamino, N-(methylsulfonyl)-N-
aminoethylamino, N-(methylsulfonyl)-N-(N',N'-
10 dimethylaminoethyl)amino, N-(N',N'-
diethylaminoethyl)-N-methylsulfonylamino, N-(N',N'-
dipropylaminoethyl)-N-methylsulfonylamino, N-
(N',N'-diisobutylaminoethyl)-N-methylsulfonylamino,
N-(N',N'-di-tert-butylmethyleaminoethyl)-N-
15 methylsulfonylamino, N-(N',N'-di(3-
ethylbutyl)aminoethyl)-N-methylsulfonylamino, N-
(N',N'-di(cyclopropylmethyl)aminoethyl)-N-
methylsulfonylamino, N-(N',N'-
di(cyclohexylmethyl)aminoethyl)-N-
20 methylsulfonylamino, N-(N',N'-di(2-
furylmethyl)aminoethyl)-N-methylsulfonylamino, N-
(N',N'-di(3-thienylmethyl)aminoethyl)-N-
methylsulfonylamino, N-(N',N'-
di(benzyl)aminoethyl)-N-methylsulfonylamino, N-
25 (methylsulfonyl)-N-isobutylamino, N-
(methylsulfonyl)-N-methylamino, N-(methylsulfonyl)-
N-phenethylamino, N-(methylsulfonyl)amino, N-
(benzylsulfonyl)amino, N-(propylsulfonyl)amino, N-
(phenylsulfonyl)amino, N-(methylsulfonyl)-N-
30 phenylpropylamino, thienylsulfonylamino, (2-
nitrophenyl)methylsulfonylamino, (2,4,6-
trimethylphenyl)sulfonylamino, (2-
cyanophenyl)sulfonylamino, N-methoxymethylcarbonyl-
N-cyclopropylmethyleamino, N-methylcarbonyl-N-

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cyclopropylmethylamino, N-phenylcarbonyl-N-
cyclopropylmethylamino, N-(3-methoxyphenylcarbonyl-
N-cyclopropylmethylamino, N-benzylcarbonyl-N-
cyclopropylmethylamino, N-cyclohexylcarbonyl-N-
5 cyclopropylmethylamino, N-thienylmethylcarbonyl-N-
cyclopropylmethylamino, N-phenylethyl-N-
cyclopropylmethylamino, N-(2-imidazolyl)-N-
cyclopropylmethylamino, N-(4-methyl-5-imidazolyl)-
N-cyclopropylmethylamino, N-(4-methyl-5-
10 imidazolylmethyl)-N-cyclopropylmethylamino, N-(4-
imidazolylmethyl)-N-cyclopropylmethylamino, N-(5-
imidazolylmethyl)-N-cyclopropylmethylamino, N-(2-
thienylmethyl)-N-cyclopropylmethylamino, N-(3-
thienylmethyl)-N-cyclopropylmethylamino, N-(3-
15 furylmethyl)-N-cyclopropylmethylamino, N-(4-
imidazolyl)-N-cyclopropylmethylamino, N-
cyclopentylcarbonyl-N-cyclopropylmethylamino, N-
cyclohexylcarbonyl-N-cyclopropylmethylamino, N-
methylthiopropyl-N-cyclopropylmethylamino, N-
20 ethylcarbonyl-N-cyclopropylmethylamino, N-
isopropylcarbonyl-N-cyclopropylmethylamino, N-
isobutylcarbonyl-N-cyclopropylmethylamino, N-ethyl-
N-cyclopropylmethylamino, N-isobutyl-N-
cyclopropylmethylamino, N-cyclopropylcarbonyl-N-
25 cyclopropylmethylamino, N,N-
di(cyclopropylmethyl)amino, N-
methoxymethylcarbonyl-N-aminoethylamino, N-
ethylcarbonyl-N-aminoethylamino, N-
isopropylcarbonyl-N-aminoethylamino, N-
30 isobutylcarbonyl-N-aminoethylamino, N-tert-
butylcarbonyl-N-aminoethylamino, N-propylcarbonyl-
N-aminoethylamino, N-pentylcarbonyl-N-
aminoethylamino, N-ethyl-N-aminoethylamino, N-
propyl-N-aminoethylamino, N-cyclopropyl-N-

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aminoethylamino, N-cyclopropylmethyl-N-
aminoethylamino, N-cyclobutylmethyl-N-
aminoethylamino, N-butyl-N-aminoethylamino, N-
pentyl-N-aminoethylamino, N-hexyl-N-
5 aminoethylamino, N-heptyl-N-aminoethylamino, N-(3-
ethylbutyl)-N-aminoethylamino, N-
cyclohexylcarbonyl-N-aminoethylamino, N-
phenylcarbonyl-N-aminoethylamino, N-(3-
methoxyphenyl)carbonyl-N-aminoethylamino, N-
10 benzylcarbonyl-N-aminoethylamino, N-
phenylethylcarbonyl-N-aminoethylamino, N-
pyridylcarbonyl-N-aminoethylamino, N-thienylmethyl-
N-aminoethylamino, aminoethylamino,
pyridylcarbonylamino, N-cyclopropylmethylamino,
15 methylcarbonylamino, methoxycarbonylamino,
trifluoromethyl, 2-hydroxyethyl, 1-hydroxyethyl,
methylaminocarbonylamino, 1,1-dioxo-isothiazolidin-
2-yl, 2-oxo-imidazolin-1-yl and 3-methyl-2-oxo-
imidazolin-1-yl;
20 wherein R¹⁵ is selected from H, C₁₋₂-haloalkyl, C₁₋₄-alkyl,
halo, -OR¹⁷, and -N(R¹⁷)₂;
preferably H and C₁₋₂-haloalkyl;
more preferably H or trifluoromethyl;
wherein R¹⁶ is selected from
25 a) 4-6 membered heterocyclyl,
b) 10 membered partially saturated heterocyclyl,
c) 5-10 membered heteroaryl,
d) C₁₋₄-aminoalkyl,
e) C₁₋₄-aminoalkylamino,
f) C₁₋₄-alkylamino-C₁₋₄-alkylamino,
30 g) C₁₋₄-alkylamino-C₁₋₄-alkyl,
h) arylamino-C₁₋₄-alkyl,
i) aryl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
j) heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-alkyl.

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- k) aryl, provided if 2-substituted aryl, is 2-substituted with amino or chloro,
- l) C₁₋₄-alkyl,
- m) aralkyl,
- 5 n) heterocyclyl-C₁₋₄-alkyl, provided R¹⁶ is not 3-methylindol-1-ylethyl,
- o) C₅₋₆-cycloalkyl,
- p) C₁₋₄-aminoalkoxy,
- q) heterocyclyl-C₁₋₄-alkoxy,
- 10 r) N-(heterocyclyl-C₁₋₄-alkyl)amino,
- s) aryl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino, and
- t) heterocyclyl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino;
- 15 preferably selected from
 - a) 4-6 membered heterocyclyl,
 - b) 10 membered partially saturated heterocyclyl,
 - c) 5-10 membered heteroaryl,
 - d) C₁₋₃-aminoalkyl,
- 20 e) C₁₋₃-aminoalkylamino,
- f) C₁₋₃-alkylamino-C₁₋₃-alkylamino,
- g) C₁₋₃-alkylamino-C₁₋₃-alkyl,
- h) phenylamino-C₁₋₃-alkyl,
- i) phenyl-C₁₋₄-alkylamino-C₁₋₃-alkyl,
- 25 j) heterocyclyl-C₁₋₃-alkylamino-C₁₋₃-alkyl,
- k) phenyl, naphthyl or tetrahydronaphthyl,
- l) C₁₋₃-alkyl,
- m) phenyl-C₁₋₂-alkyl,
- 30 n) 5-10-membered saturated or partially unsaturated heterocyclymethyl,
- o) optionally substituted 5-6 membered heteroaryl-C₁₋₄-alkyl,
- p) C₅₋₆-cycloalkyl,
- q) C₁₋₃-aminoalkoxy,

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- r) [5- or 6- membered heterocyclyl]-C₁₋₃-alkoxy,
- s) N-(5-10-membered heterocyclyl-C₁₋₃-alkyl)amino,
- t) phenyl-C₁₋₂-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino,
5 and
 - u) 5- or 6- membered heterocyclyl-C₁₋₃-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino;
more preferably N-(piperidylmethyl)amino,
- 10 aminopropylamino, aminomethyl, aminoethyl, aminopropyl, N-methylaminomethyl, N-(4-chlorophenyl)aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl, 2-aminoethyl, aminoproxy, pyrrolidinylmethoxy, N-methylaminoethylamino, 3-aminocyclopentyl, 4-aminocyclohexyl, 1-aminocyclohexyl, 2-indolyl, octahydro-indolyl, 1-methylindol-2-yl, 3-pyridyl, 2-pyridyl, N-methylbenzopyrrolyl, 5-benzopyrrolyl, 2-benzofuran, benzodioxolyl, 2-benzothienyl, 4-imidazolylmethyl,
15 3-azetidinyl
 - optionally N-substituted with a substituent selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, cyclohexylmethyl and benzyl,
- 20 6-quinolyl, 2-quinolyl, 3-isoquinolyl, tetrahydroisoquinolyl, N-methylpyrrolidin-2-yl, pyrrolidin-2-yl, 5-oxopyrrolidin-2-yl, 3-phenylpyrrolidin-2-yl, (1-methyl-5-oxo-2-(pyridin-3-yl)-pyrrolidin-3-yl)methyl, thienyl, 4-piperidyl,
25 4-piperidylmethyl, N-methyl-4-piperidyl, N-methyl-2-piperidyl, N-ethyl-4-piperidyl, N-isobutyl-4-piperidyl, 3-piperidyl, 3-(aminomethyl)phenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl,
30 2-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3-

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chlorophenyl, 2-chlorophenyl, 3,4-dichlorophenyl,
4-fluorophenyl, 3-fluorophenyl, 2-aminophenyl, 3-
aminophenyl, isopropyl, 4-chlorophenylmethyl,
benzyl, phenyl-2-hydroxyethyl, 1-(amino)benzyl, 2-
5 (1,2,3,4-tetrahydronaphthyl), naphthyl, (2-
benzylamino)ethyl, imidazol-4-yl-(1-amino)ethyl,
phenyl-1-(methylamino)ethyl and phenyl-1-
(amino)ethyl;
wherein R¹⁷ is selected from H, C₁₋₄-alkyl, C₃₋₇-cycloalkyl-
10 (CH₂)_n-, and aryl-(CH₂)_n;
preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, and -
(CH₂)_n-phenyl;
more preferably H, methyl, ethyl, propyl, isopropyl,
cyclopropyl, cyclopropylmethyl, cyclopentyl,
15 cyclopentylmethyl, cyclohexyl, cyclohexylmethyl,
phenylpropyl, phenylethyl, benzyl and phenyl;
wherein R¹⁹ is selected from H, R²³SO₂-, C₁₋₆-alkyl, C₃₋₇-
cycloalkyl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-
20 alkyl, C₃₋₇-cycloalkylamino-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₁₋₆-
alkylamino-C₁₋₆-alkyl, heteroarylarnino-C₁₋₆-alkyl,
heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, arylamino-C₁₋₆-alkyl,
aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, heteroaryloxy-C₁₋₆-alkyl,
25 heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryloxy-C₁₋₆-alkyl,
aryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-
alkylthio-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₁₋₆-
alkylcarbonyl, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxy-C₁₋₆-
alkylcarbonyl, C₁₋₆-alkylaminocarbonyl, arylcarbonyl,
aralkylcarbonyl, C₃₋₇-cycloalkylcarbonyl, C₃₋₇-cycloalkyl-
30 C₁₋₆-alkylcarbonyl, heteroaryl-C₁₋₆-alkylcarbonyl and
heteroarylcarbonyl;
preferably H, R²³SO₂-, C₁₋₆-alkyl, amino-C₁₋₃-alkyl, C₁₋₆-
alkylamino-C₁₋₃-alkyl, C₃₋₅-cycloalkylamino-C₁₋₃-alkyl,
C₃₋₅-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-
alkylthio-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl,

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heteroaryl-amino-C₁₋₃-alkyl, 5-6 membered heteroaryl-C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl,
phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6 membered
heteroaryloxy-C₁₋₃-alkyl, phenoxy-C₁₋₃-alkyl,
5 hydroxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-
alkylcarbonyl, C₁₋₃-alkoxycarbonyl, C₁₋₃-alkoxy-C₁₋₃-
alkylcarbonyl, C₁₋₃-alkylaminocarbonyl, C₃₋₆-
cycloalkylcarbonyl, C₃₋₆-cycloalkyl-C₁₋₃-
alkylcarbonyl, phenylcarbonyl, phenyl-C₁₋₃-
10 alkylcarbonyl, 5- or 6- membered heteroaryl-C₁₋₃-
alkylcarbonyl, 5- or 6- membered heteroarylcarbonyl
and -(CH₂)_n-C₃₋₅-cycloalkyl optionally substituted
with C₁₋₂-alkoxycarbonyl;
more preferably H, R²³SO₂-, methyl, ethyl, propyl,
15 isopropyl, isopentyl, 3-ethylbutyl,
hydroxymethyl, hydroxyethyl, cyclopropylmethyl,
1-(ethoxycarbonyl)cycloprop-2-ylmethyl, R²³SO₂-,
aminomethyl, aminoethyl, dimethylaminoethyl,
diethylaminoethyl, dipropylaminoethyl, di-
20 isobutylaminoethyl, di-(tert-
butylmethyl)aminoethyl, di-(3-
ethylbutyl)aminoethyl, di-
(cyclohexylmethyl)aminoethyl,
furylmethylaminoethyl, thiienylmethylethylaminoethyl,
benzylaminoethyl, di(furylmethyl)aminoethyl,
25 di(cyclopropylmethyl)aminoethyl,
di(thienylmethyl)aminoethyl,
di(benzyl)aminoethyl, phenylmethoxyethyl,
pyridyloxymethyl, methylthiopropyl,
30 methylcarbonyl, ethylcarbonyl, propylcarbonyl,
isopropylcarbonyl, isobutylcarbonyl,
butylcarbonyl, tert-butylcarbonyl,
pentylcarbonyl, cyclopentylcarbonyl,
cyclopropylcarbonyl, cyclobutylcarbonyl,

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cyclohexylcarbonyl, methoxycarbonyl,
methoxymethylcarbonyl, ethoxycarbonyl,
propoxycarbonyl, methylaminocarbonyl,
ethylaminocarbonyl, propylaminocarbonyl,
5 optionally substituted thiethylmethylcarbonyl,
optionally substituted benzylcarbonyl, optionally
substituted phenylethylcarbonyl, optionally
substituted phenylcarbonyl and optionally
substituted pyridylcarbonyl;

10 wherein R²⁰ is selected from H, C₁₋₈-alkyl, C₃₋₇-cycloalkyl-
(CH₂)_n-, C₁₋₃-alkylsulfonyl, amino-C₁₋₃-alkyl, heterocyclyl-
(CH₂)_n-, and aryl-(CH₂)_n;
preferably H, C₁₋₇-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl, -(CH₂)_n-
5-6-membered heterocyclyl, C₁₋₃-alkylsulfonyl, amino-
15 C₁₋₃-alkyl and -(CH₂)_n-phenyl;
more preferably H, methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, hexyl,
heptyl, cyclopropylmethyl, cyclobutylmethyl,
cyclopentylmethyl, cyclohexylmethyl, cyclopropyl,
20 cyclohexyl, methylsulfonyl, aminoethyl,
optionally substituted phenyl, optionally
substituted imidazolyl, optionally substituted
imidazolylmethyl, optionally substituted
thienylmethyl, optionally substituted
thienylmethyl, optionally substituted
furylmethyl, optionally substituted
25 pyrrolidinylmethyl, optionally substituted
pyridylmethyl, optionally substituted
thienylmethyl, optionally substituted benzyl,
optionally substituted phenylethyl and optionally
substituted phenylpropyl;

30 alternatively R¹⁹ and R²⁰ together with the nitrogen atom
form a 4-8 membered heterocyclic ring;
preferably a 4-7 membered heterocyclic ring;

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more preferably a heterocyclic ring selected from triazolyl, tetrazolyl, 2-pyridone, oxo-pyrrolidinyl, 2-oxo-piperidinyl, 4,5-dihydro-2-oxo-oxazolyl, 1,1-dioxo-isothiazolidin-2-yl, 2-oxo-imidazolin-1-yl, 3-methyl-2-oxo-imidazolin-1-yl, piperidinyl optionally substituted with one or more substituents selected from methyl, ethyl, propyl, and isopropyl,

10 piperazinyl optionally substituted with one or more substituents selected from methyl, ethyl, propyl, and isopropyl,

imidazolyl optionally substituted with one or more substituents selected from methyl, ethyl, propyl, and isopropyl, and

15 pyrrolidinyl optionally substituted with one or more substituents selected from methyl, ethyl, propyl, and isopropyl;

wherein R²¹ is selected from H, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, 20 amino-C₁₋₆-alkyl, heterocyclyl-(CH₂)_n-, C₃₋₇-cycloalkyl-(CH₂)_n-, and aryl-(CH₂)_n-, preferably H, C₁₋₃-alkyl, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, amino-C₁₋₃-alkyl, -(CH₂)_n-[5- or 6-membered heterocyclyl], - 25 (CH₂)_n-C₅₋₆-cycloalkyl, and -(CH₂)_n-phenyl; more preferably H, methyl, ethyl, propyl, isopropyl, allyl, methylthioethyl, methylthiomethyl, methylcarbonylaminoethyl, methylcarbonylaminomethyl, aminomethyl, aminoethyl, 1-methylpyrrolidinylethyl, 30 piperidinylethyl, pyridyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, 4-chlorophenylmethyl, 4-phenoxyphenylethyl, benzyl and phenylethyl;

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wherein R²² is selected from H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₇-cycloalkyl, -(CH₂)_n-heterocyclyl and -(CH₂)_n-aryl; preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, -(CH₂)_n-[5- or 6- membered heterocyclyl] and -(CH₂)_n-phenyl;

5 more preferably H or methyl; alternatively R²¹ and R²² together with the amide nitrogen atom form a 4-7 membered saturated heterocyclic ring; preferably a 5-6 membered heterocyclic ring; more preferably a ring selected from pyrrolidinyl, morpholino, piperidinyl, piperazinyl, 4-acetylpirerazinyl and 4-methylpirerazinyl;

10 wherein R²³ is selected from H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₇-cycloalkyl, -(CH₂)_n-heterocyclyl and -(CH₂)_n-aryl; preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, -(CH₂)_n-[5- or 6- membered heterocyclyl] and -(CH₂)_n-phenyl;

15 more preferably H, methyl, ethyl, propyl, optionally substituted thienyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted phenylethyl and optionally substituted phenylpropyl;

20 wherein n is 0, 1, 2 or 3; wherein m is 0, 1 or 2; and wherein aryl, heterocyclyl and cycloalkyl are optionally substituted with one or more substituents selected from C₁₋₂-haloalkyl, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, chloro, fluoro, -OR¹⁷, -NR¹⁷SO₂R¹⁷, N(R¹⁷)₂, cyano, -COR¹⁷, -C(R¹⁷)₂N(R¹⁷)₂, nitro, -SO₂N(R¹⁷)₂, -S(O)_mR¹⁷, and C₁₋₃-haloalkoxy;

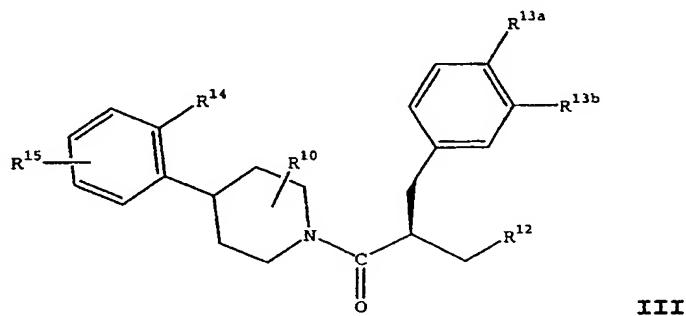
25 preferably with one or more substituents selected from C₁₋₂-haloalkyl, C₁₋₂-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, chloro, fluoro, -OR¹⁷, -NR¹⁷SO₂R¹⁷, N(R¹⁷)₂, cyano, -COR¹⁷, -C(R¹⁷)₂N(R¹⁷)₂, nitro, -SO₂N(R¹⁷)₂, -S(O)_mR¹⁷, and C₁₋₂-haloalkoxy;

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more preferably with one or more substituents selected from trifluoromethyl, methyl, nitro, cyano, chloro, methoxy, phenoxy, acetyl, amino, dimethylamino and aminomethyl.

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The invention also relates to compounds of Formula III



10 wherein R¹⁰ is selected from H, chloro or fluoro; or wherein R¹⁰ is a C₁₋₄-alkylene bridge; preferably H; wherein R¹² is selected from optionally substituted phenyl-C₁₋₂-alkylenyl, optionally substituted 5-10 membered

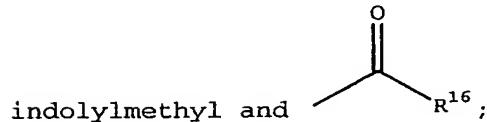
15 heteroaryl and R¹⁶; provided the optionally substituted heterocyclyl is not nitro substituted;

R¹⁶, optionally substituted phenyl-C₁-alkyl, and optionally substituted 5-10-membered heterocyclyl;

20 more preferably oxazolylpyridyl, 4-(N,N-dimethylamino)phenylmethyl, 2,2-dimethyl-

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oxazolidinyl, benzodioxanylmethyl, pyridylmethyl,



- wherein R^{13a} and R^{13b} are independently selected from H,
fluoro, iodo, bromo, chloro, C₁₋₂-alkyl, C₁₋₂-haloalkyl,
5 phenyl, and C₁₋₂-alkoxy; or wherein R^{13a} and R^{13b} together
form an C₁₋₄-alkenyl bridge;
preferably R^{13a} is selected from H, bromo, chloro,
phenyl, trifluoromethyl and methoxy;
more preferably H and chloro;
- 10 preferably R^{13b} is H;
wherein R¹⁴ is selected from R¹⁹R²⁰N-, R¹⁹R²⁰N-C₁₋₄-alkyl,
(R²¹R²²N-) (O=)C-, C₁₋₄-haloalkyl, C₂₋₄-hydroxyalkyl,
heterocyclyloxy-C₁₋₄-alkyl, aryloxy-C₁₋₄-alkyl and C₁₋₄-
alkoxycarbonyl;
- 15 preferably trifluoromethyl, 2-hydroxyethyl, 1-
hydroxyethyl, R¹⁹R²⁰N-, R¹⁹R²⁰N-C₁₋₂-alkyl and (R²¹R²²N-
) (O=)C-;
more preferably N-pyrrolidinylcarbonyl, N-
- 20 morpholinocarbonyl, N-
piperidinylethylaminocarbonyl, benzylaminocarbonyl,
N-methyl-N-benzylaminocarbonyl,
aminoethylaminocarbonyl, pyridylaminocarbonyl,
methylthioethylaminocarbonyl,
methylcarbonylaminoethylaminocarbonyl, 1-
- 25 methylpyrrolidinylethylaminocarbonyl,
phenethylaminocarbonyl, phenylaminocarbonyl,
cyclohexylmethylaminocarbonyl, N-methyl-N-
phenethylaminocarbonyl, N,N-dimethylaminocarbonyl,
4-chlorophenylmethylaminocarbonyl,
- 30 phenoxyphenethylaminocarbonyl, allylaminocarbonyl,
4-methylpiperazinylcarbonyl, 4-
acetyl piperazinylcarbonyl, isopropylaminocarbonyl,

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1 - (N-cyclopropylmethylamino)ethyl, 1 - (N-methyl-N-methylcarbonylamino)ethyl, 1 - (N-isopropylamino)ethyl, 1 - (N-isobutyl-N-methylamino)ethyl, N-cyclopropylmethyl-N-propylaminomethyl, N,N-dicyclopropylmethylaminomethyl, 1 - (N-propyl-N-methylamino)ethyl, 1 - (N-methyl-N-methylsulfonylamino)ethyl, triazolylmethyl, imidazol-1-ylmethyl, 2-isopropylimidazol-1-yl-methyl, 2-propylimidazol-1-yl-methyl, 2-oxo-pyrid-1-yl-methyl, 3-pyridyl-oxymethyl, 2-methylimidazol-1-yl-methyl, tetrazolylmethyl, 2,5-dimethylpyrrolidin-1-ylmethyl, 2-oxo-pyrrolidin-1-yl-methyl, 2-oxo-piperidin-1-yl-methyl, 4,5-dihydro-2-oxo-oxazol-3-yl-methyl, pyrrolidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, piperazin-1-yl-methyl, 4-methylpiperazin-1-yl-methyl, piperidin-1-yl-methyl, 1 - (N-ethyl-N-methylamino)ethyl, 1 - (N,N-dipropylamino)ethyl, 1 - (N,N-diisopropylamino)ethyl, 1 - (N-(1-ethoxycarbonyl)cycloprop-2-ylmethyl-N-methylamino)ethyl, 1 - (N-(2-methylbutyl)-N-methylamino)ethyl, 1 - (N-(4-methylcarbonylaminophenyl)methyl-N-methylamino)ethyl, 1 - (N,N-dimethylamino)ethyl, 1 - (N-methylamino)ethyl, 1 - (N,N-dimethylaminomethyl, N-cyclopropylmethyl-N-methylsulfonylamino)ethyl, 1 - (N-(3-thienyl)methyl-N-methylamino)ethyl, 1 - (N-phenylmethoxyethyl-N-methylamino)ethyl, 1 - (N-(2-methoxyphenyl)methyl-N-methylamino)ethyl, 1 - (N-(4-pyridyl)methyl-N-methylamino)ethyl, 1 - (N-(2-pyrrolidinyl)methyl-N-methylamino)ethyl, 1 - (N-(3-methoxyphenyl)methyl-N-methylamino)ethyl, 1 - (N-(4-methoxyphenyl)methyl-N-methylamino)ethyl, 1 - (N-

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benzyl-N-methylamino)ethyl, 1-(N-methyl-N-
aminoethylamino)ethyl, 1-(N-cyclohexylmethyl-N-
methylamino)ethyl, N,N-dimethylaminomethyl, N-(1-
hydroxyethyl)-N-methylaminomethyl, N-(1-
5 hydroxyethyl)-N-methylaminomethyl, N-propyl-N-
methylsulfonylamino, N-(methylsulfonyl)-N-
propylamino, N-(methylsulfonyl)-N-
cyclopropylmethylamino, N-(methylsulfonyl)-N-
aminoethylamino, N-(methylsulfonyl)-N-(N',N'-
10 dimethylaminoethyl)amino, N-(N',N'-
diethylaminoethyl)-N-methylsulfonylamino, N-(N',N'-
dipropylaminoethyl)-N-methylsulfonylamino, N-
(N',N'-diisobutylaminoethyl)-N-methylsulfonylamino,
N-(N',N'-di-tert-butylmethylaminoethyl)-N-
15 methylsulfonylamino, N-(N',N'-di(3-
ethylbutyl)aminoethyl)-N-methylsulfonylamino, N-
(N',N'-di(cyclopropylmethyl)aminoethyl)-N-
methylsulfonylamino, N-(N',N'-
di(cyclohexylmethyl)aminoethyl)-N-
20 methylsulfonylamino, N-(N',N'-di(2-
furylmethyl)aminoethyl)-N-methylsulfonylamino, N-
(N',N'-di(3-thienylmethyl)aminoethyl)-N-
methylsulfonylamino, N-(N',N'-
di(benzyl)aminoethyl)-N-methylsulfonylamino, N-
25 (methylsulfonyl)-N-isobutylamino, N-
(methylsulfonyl)-N-methylamino, N-(methylsulfonyl)-
N-phenethylamino, N-(methylsulfonyl)amino, N-
(benzylsulfonyl)amino, N-(propylsulfonyl)amino, N-
(phenylsulfonyl)amino, N-(methylsulfonyl)-N-
30 phenylpropylamino, thienylsulfonylamino, (2-
nitrophenyl)methylsulfonylamino, (2,4,6-
trimethylphenyl)sulfonylamino, (2-
cyanophenyl)sulfonylamino, N-methoxymethylcarbonyl-
N-cyclopropylmethylamino, N-methylcarbonyl-N-

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cyclopropylmethylamino, N-phenylcarbonyl-N-
cyclopropylmethylamino, N-(3-methoxyphenylcarbonyl-
N-cyclopropylmethylamino, N-benzylcarbonyl-N-
cyclopropylmethylamino, N-cyclohexylcarbonyl-N-
5 cyclopropylmethylamino, N-thienylmethylcarbonyl-N-
cyclopropylmethylamino, N-phenylethyl-N-
cyclopropylmethylamino, N-(2-imidazolyl)-N-
cyclopropylmethylamino, N-(4-methyl-5-imidazolyl)-
N-cyclopropylmethylamino, N-(4-methyl-5-
10 imidazolylmethyl)-N-cyclopropylmethylamino, N-(4-
imidazolylmethyl)-N-cyclopropylmethylamino, N-(5-
imidazolylmethyl)-N-cyclopropylmethylamino, N-(2-
thienylmethyl)-N-cyclopropylmethylamino, N-(3-
thienylmethyl)-N-cyclopropylmethylamino, N-(3-
15 furylmethyl)-N-cyclopropylmethylamino, N-(4-
imidazolyl)-N-cyclopropylmethylamino, N-
cyclopentylcarbonyl-N-cyclopropylmethylamino, N-
cyclohexylcarbonyl-N-cyclopropylmethylamino, N-
methylthiopropyl-N-cyclopropylmethylamino, N-
20 ethylcarbonyl-N-cyclopropylmethylamino, N-
isopropylcarbonyl-N-cyclopropylmethylamino, N-
isobutylcarbonyl-N-cyclopropylmethylamino, N-ethyl-
N-cyclopropylmethylamino, N-isobutyl-N-
cyclopropylmethylamino, N-cyclopropylcarbonyl-N-
25 cyclopropylmethylamino, N,N-
di(cyclopropylmethyl)amino, N-
methoxymethylcarbonyl-N-aminoethylamino, N-
ethylcarbonyl-N-aminoethylamino, N-
isopropylcarbonyl-N-aminoethylamino, N-
30 isobutylcarbonyl-N-aminoethylamino, N-tert-
butylcarbonyl-N-aminoethylamino, N-propylcarbonyl-
N-aminoethylamino, N-pentylcarbonyl-N-
aminoethylamino, N-ethyl-N-aminoethylamino, N-
propyl-N-aminoethylamino, N-cyclopropyl-N-

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aminoethylamino, N-cyclopropylmethyl-N-
aminoethylamino, N-cyclobutylmethyl-N-
aminoethylamino, N-butyl-N-aminoethylamino, N-
pentyl-N-aminoethylamino, N-hexyl-N-
5 aminoethylamino, N-heptyl-N-aminoethylamino, N-(3-
ethylbutyl)-N-aminoethylamino, N-
cyclohexylcarbonyl-N-aminoethylamino, N-
phenylcarbonyl-N-aminoethylamino, N-(3-
methoxyphenyl)carbonyl-N-aminoethylamino, N-
10 benzylcarbonyl-N-aminoethylamino, N-
phenylethylcarbonyl-N-aminoethylamino, N-
pyridylcarbonyl-N-aminoethylamino, N-thienylmethyl-
N-aminoethylamino, aminoethylamino,
pyridylcarbonylamino, N-cyclopropylmethylamino,
15 methylcarbonylamino, methoxycarbonylamino,
trifluoromethyl, 2-hydroxyethyl, 1-hydroxyethyl,
methylaminocarbonylamino, 1,1-dioxo-isothiazolidin-
2-yl, 2-oxo-imidazolin-1-yl and 3-methyl-2-oxo-
imidazolin-1-yl;
20 wherein R¹⁵ is selected from H, C₁₋₂-haloalkyl, C₁₋₄-alkyl,
halo, -OR¹⁷, and -N(R¹⁷)₂;
preferably H and C₁₋₂-haloalkyl;
more preferably H or trifluoromethyl;
wherein R¹⁶ is selected from
25 a) 4-6 membered heterocyclyl,
b) 10 membered partially saturated heterocyclyl,
c) 5-10 membered heteroaryl,
d) C₁₋₄-aminoalkyl,
e) C₁₋₄-aminoalkylamino,
f) C₁₋₄-alkylamino-C₁₋₄-alkylamino,
30 g) C₁₋₄-alkylamino-C₁₋₄-alkyl,
h) arylamino-C₁₋₄-alkyl,
i) aryl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
j) heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,

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- k) aryl, provided if 2-substituted aryl, is 2-substituted with amino or chloro,
- l) C₁₋₄-alkyl,
- m) aralkyl,
- 5 n) heterocycl-C₁₋₄-alkyl, provided R¹⁶ is not 3-methylindol-1-ylethyl,
- o) C₅₋₆-cycloalkyl,
- p) C₁₋₄-aminoalkoxy,
- q) heterocycl-C₁₋₄-alkoxy,
- 10 r) N-(heterocycl-C₁₋₄-alkyl)amino,
- s) aryl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino, and
- t) heterocycl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino;
- 15 preferably selected from
 - a) 4-6 membered heterocycl,
 - b) 10 membered partially saturated heterocycl,
 - c) 5-10 membered heteroaryl,
 - d) C₁₋₃-aminoalkyl,
 - e) C₁₋₃-aminoalkylamino,
 - 20 f) C₁₋₃-alkylamino-C₁₋₃-alkylamino,
 - g) C₁₋₃-alkylamino-C₁₋₃-alkyl,
 - h) phenylamino-C₁₋₃-alkyl,
 - i) phenyl-C₁₋₄-alkylamino-C₁₋₃-alkyl,
 - 25 j) heterocycl-C₁₋₃-alkylamino-C₁₋₃-alkyl,
 - k) phenyl, naphthyl or tetrahydronaphthyl,
 - l) C₁₋₃-alkyl,
 - m) phenyl-C₁₋₂-alkyl,
 - n) 5-10-membered saturated or partially unsaturated
 - 30 heterocyclmethyl,
 - o) 5-6 membered heteroaryl-C₁₋₄-alkyl,
 - p) C₅₋₆-cycloalkyl,
 - q) C₁₋₃-aminoalkoxy,
 - r) [5- or 6-membered heterocycl]-C₁₋₃-alkoxy,

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- s) N-(5-10-membered heterocyclyl-C₁₋₃-alkyl)amino,
- t) phenyl-C₁₋₂-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino, and
- 5 u) 5- or 6-membered heterocyclyl-C₁₋₃-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino;
- more preferably N-(piperidylmethyl)amino,
- aminopropylamino, aminomethyl, aminoethyl,
- 10 aminopropyl, N-methylaminomethyl, N-(4-chlorophenyl)aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl, 2-aminoethyl, aminoproxy, pyrrolidinylmethoxy, N-methylaminoethylamino, 3-aminocyclopentyl, 4-aminocyclohexyl, 1-aminocyclohexyl, 2-indolyl, octahydro-indolyl, 1-methylindol-2-yl, 3-pyridyl, 2-pyridyl, N-methylbenzopyrrolyl, 5-benzopyrrolyl, 2-benzofuran, benzodioxoly1, 2-benzothienyl, 4-imidazolylmethyl, 3-azetidinyl
- 15 20 optionally N-substituted with a substituent selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, cyclohexylmethyl and benzyl,
- 6-quinolyl, 2-quinolyl, 3-isoquinolyl,
- 25 tetrahydroisoquinolyl, N-methylpyrrolidin-2-yl, pyrrolidin-2-yl, 5-oxopyrrolidin-2-yl, 3-phenylpyrrolidin-2-yl, (1-methyl-5-oxo-2-(pyridin-3-yl)-pyrrolidin-3-yl)methyl, thienyl, 4-piperidyl, 4-piperidylmethyl, N-methyl-4-piperidyl, N-methyl-2-piperidyl, N-ethyl-4-piperidyl, N-isobutyl-4-piperidyl, 3-piperidyl, 3-(aminomethyl)phenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4-dichlorophenyl,

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4-fluorophenyl, 3-fluorophenyl, 2-aminophenyl, 3-aminophenyl, isopropyl, 4-chlorophenylmethyl, benzyl, phenyl-2-hydroxyethyl, 1-(amino)benzyl, 2-(1,2,3,4-tetrahydronaphthyl), naphthyl, (2-benzylamino)ethyl, imidazol-4-yl-(1-amino)ethyl, phenyl-1-(methylamino)ethyl and phenyl-1-(amino)ethyl;

5 wherein R¹⁷ is selected from H, C₁₋₄-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, and aryl-(CH₂)_n-, preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, and -

10 (CH₂)_n-phenyl; more preferably H, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenylpropyl, phenylethyl, benzyl and phenyl;

15 wherein R¹⁹ is selected from H, R²³SO₂-, C₁₋₆-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-alkyl, C₃₋₇-cycloalkylamino-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, heteroarylamino-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, arylamino-C₁₋₆-alkyl,

20 aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, heteroaryloxy-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryloxy-C₁₋₆-alkyl, aryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkylcarbonyl, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxy-C₁₋₆-alkylcarbonyl, C₁₋₆-alkylaminocarbonyl, arylcarbonyl, aralkylcarbonyl, C₃₋₇-cycloalkylcarbonyl, C₃₋₇-cycloalkyl-C₁₋₆-alkylcarbonyl, heteroaryl-C₁₋₆-alkylcarbonyl and heteroarylcarbonyl;

25 preferably H, R²³SO₂-, C₁₋₆-alkyl, amino-C₁₋₃-alkyl, C₁₋₆-alkylamino-C₁₋₃-alkyl, C₃₋₅-cycloalkylamino-C₁₋₃-alkyl, C₃₋₅-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, heteroarylamino-C₁₋₃-alkyl, 5-6 membered heteroaryl-

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C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl,
phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6 membered
heteroaryloxy-C₁₋₃-alkyl, phenoxy-C₁₋₃-alkyl,
hydroxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-
5 alkylcarbonyl, C₁₋₃-alkoxycarbonyl, C₁₋₃-alkoxy-C₁₋₃-
alkylcarbonyl, C₁₋₃-alkylaminocarbonyl, C₃₋₆-
cycloalkylcarbonyl, C₃₋₆-cycloalkyl-C₁₋₃-
alkylcarbonyl, phenylcarbonyl, phenyl-C₁₋₃-
alkylcarbonyl, 5- or 6- membered heteroaryl-C₁₋₃-
10 alkylcarbonyl, 5- or 6- membered heteroarylcarbonyl
and -(CH₂)_n-C₃₋₅-cycloalkyl optionally substituted
with C₁₋₂-alkoxycarbonyl;
more preferably H, R²³SO₂-, methyl, ethyl, propyl,
isopropyl, isopentyl, 3-ethylbutyl,
15 hydroxymethyl, hydroxyethyl, cyclopropylmethyl,
1-(ethoxycarbonyl)cycloprop-2-ylmethyl, R²³SO₂-,
aminomethyl, aminoethyl, dimethylaminoethyl,
diethylaminoethyl, dipropylaminoethyl, di-
isobutylaminoethyl, di-(tert-
20 butylmethyl)aminoethyl, di-(3-
ethylbutyl)aminoethyl, di-
(cyclohexylmethyl)aminoethyl,
furylmethylaminoethyl, thienylmethylaminoethyl,
benzylaminoethyl, di(furylmethyl)aminoethyl,
25 di(cyclopropylmethyl)aminoethyl,
di(thienylmethyl)aminoethyl,
di(benzyl)aminoethyl, phenylmethoxyethyl,
pyridyloxymethyl, methylthiopropyl,
methylcarbonyl, ethylcarbonyl, propylcarbonyl,
isopropylcarbonyl, isobutylcarbonyl,
30 butylcarbonyl, tert-butylcarbonyl,
pentylcarbonyl, cyclopentylcarbonyl,
cyclopropylcarbonyl, cyclobutylcarbonyl,
cyclohexylcarbonyl, methoxycarbonyl,

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methoxymethylcarbonyl, ethoxycarbonyl,
propoxycarbonyl, methylaminocarbonyl,
ethylaminocarbonyl, propylaminocarbonyl,
optionally substituted thi enylmethylcarbonyl,
5 optionally substituted benzylcarbonyl, optionally
 substituted phenylethylcarbonyl, optionally
 substituted phenylcarbonyl and optionally
 substituted pyridylcarbonyl;
wherein R²⁰ is selected from H, C₁₋₈-alkyl, C₃₋₇-cycloalkyl-
10 (CH₂)_n-, C₁₋₃-alkylsulfonyl, amino-C₁₋₃-alkyl, heterocyclyl-
 (CH₂)_n-, and aryl-(CH₂)_n;
 preferably H, C₁₋₇-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl, -(CH₂)_n-
 5-6-membered heterocyclyl, C₁₋₃-alkylsulfonyl, amino-
 C₁₋₃-alkyl and -(CH₂)_n-phenyl;
15 more preferably H, methyl, ethyl, propyl,
 isopropyl, butyl, isobutyl, pentyl, hexyl,
 heptyl, cyclopropylmethyl, cyclobutylmethyl,
 cyclopentylmethyl, cyclohexylmethyl, cyclopropyl,
 cyclohexyl, methylsulfonyl, aminoethyl,
20 optionally substituted phenyl, optionally
 substituted imidazolyl, optionally substituted
 imidazolylmethyl, optionally substituted
 thienylmethyl, optionally substituted
 furylmethyl, optionally substituted
25 pyrrolidinylmethyl, optionally substituted
 pyridylmethyl, optionally substituted
 thienylmethyl, optionally substituted benzyl,
 optionally substituted phenylethyl and optionally
 substituted phenylpropyl;
30 alternatively R¹⁹ and R²⁰ together with the nitrogen atom
 form a 4-8 membered heterocyclic ring;
 preferably a 4-7 membered heterocyclic ring;
 more preferably a heterocyclic ring selected from
 triazolyl, tetrazolyl, 2-pyridone, oxo-

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pyrrolidinyl, 2-oxo-piperidinyl, 4,5-dihydro-2-oxo-
oxazolyl, 1,1-dioxo-isothiazolidin-2-yl, 2-oxo-
imidazolin-1-yl, 3-methyl-2-oxo-imidazolin-1-yl,
piperidinyl optionally substituted with
5 one or more substituents selected from methyl,
ethyl, propyl, and isopropyl,
piperazinyl optionally substituted with one or more
substituents selected from methyl, ethyl, propyl,
and isopropyl,
10 imidazolyl optionally substituted with one or more
substituents selected from methyl, ethyl, propyl,
and isopropyl, and
pyrrolidinyl optionally substituted with one or
more substituents selected from methyl, ethyl,
15 propyl, and isopropyl;
wherein R²¹ is selected from H, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₁₋₆-
alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl,
amino-C₁₋₆-alkyl, heterocyclyl-(CH₂)_n-, C₃₋₇-cycloalkyl-
(CH₂)_n-, and aryl-(CH₂)_n;
20 preferably H, C₁₋₃-alkyl, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-
alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, amino-C₁₋₃-
alkyl, -(CH₂)_n-[5- or 6- membered heterocyclyl], -
(CH₂)_n-C₅₋₆-cycloalkyl, and -(CH₂)_n-phenyl;
more preferably H, methyl, ethyl, propyl,
25 isopropyl, allyl, methylthioethyl,
methylthiomethyl, methylcarbonylaminoethyl,
methylcarbonylaminomethyl, aminomethyl,
aminoethyl, 1-methylpyrrolidinylethyl,
piperidinylethyl, pyridyl, cyclopentylmethyl,
30 cyclohexylmethyl, phenyl, 4-chlorophenylmethyl,
4-phenoxyphenylethyl, benzyl and phenylethyl;
wherein R²² is selected from H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₇-
cycloalkyl, -(CH₂)_n-heterocyclyl and -(CH₂)_n-aryl;

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preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, -(CH₂)_n-
[5- or 6- membered heterocyclyl] and -(CH₂)_n-phenyl;
more preferably H or methyl;
alternatively R²¹ and R²² together with the amide nitrogen
5 atom form a 4-7 membered saturated heterocyclic ring;
preferably a 5-6 membered heterocyclic ring;
more preferably a ring selected from pyrrolidinyl,
morpholino, piperidinyl, piperazinyl, 4-
acetyl piperazinyl and 4-methyl piperazinyl;
10 wherein R²³ is selected from H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₇-
cycloalkyl, -(CH₂)_n-heterocyclyl and -(CH₂)_n-aryl;
preferably H, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, -(CH₂)_n-
[5- or 6- membered heterocyclyl] and -(CH₂)_n-phenyl;
more preferably H, methyl, ethyl, propyl,
15 optionally substituted thienyl, optionally
substituted phenyl, optionally substituted
benzyl, optionally substituted phenylethyl and
optionally substituted phenylpropyl;
wherein n is 0, 1, 2 or 3;
20 wherein m is 0, 1 or 2; and
wherein aryl, heterocyclyl are optionally substituted with
one or more substituents selected from C₁₋₂-haloalkyl, C₁₋
3-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, chloro, fluoro, -OR¹⁷, -
NR¹⁷SO₂R¹⁷, N(R¹⁷)₂, cyano, -COR¹⁷, -C(R¹⁷)₂N(R¹⁷)₂, nitro, -
25 SO₂N(R¹⁷)₂, -S(O)_mR¹⁷, and C₁₋₃-haloalkoxy;
preferably with one or more substituents selected from
C₁₋₂-haloalkyl, C₁₋₂-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, chloro,
fluoro, -OR¹⁷, -NR¹⁷SO₂R¹⁷, N(R¹⁷)₂, cyano, -COR¹⁷, -
C(R¹⁷)₂N(R¹⁷)₂, nitro, -SO₂N(R¹⁷)₂, -S(O)_mR¹⁷, and C₁₋₂-
30 haloalkoxy;
more preferably with one or more substituents
selected from trifluoromethyl, methyl, nitro, cyano,
chloro, methoxy, phenoxy, acetyl, amino,
dimethylamino and aminomethyl.

Indications

Compounds of the present invention would be useful for, but not limited to, the prevention or treatment of 5 obesity and obesity-related diseases. The compounds of the invention have MCR agonist activity, including MCR4 agonist activity.

Compounds of formula I are MCR agonists and as such are useful in the treatment, control or prevention of 10 diseases, disorders or conditions responsive to the activation of one or more of the MCRs including, but are not limited to, MCR1, MCR2, MCR3, MCR4, and/or MCR5. Such diseases, disorders or conditions include, but are not limited to, obesity (by reducing appetite, increasing 15 metabolic rate, reducing fat intake or reducing carbohydrate craving), diabetes mellitus (by enhancing glucose tolerance, decreasing insulin resistance), hypertension, hyperlipidemia, osteoarthritis, cancer, gall bladder disease, sleep apnea, depression, anxiety, compulsion, 20 neuroses, insomnia/sleep disorder, substance abuse, pain, male and female sexual dysfunction (including impotence, loss of libido and erectile dysfunction), fever, inflammation, immunomodulation, rheumatoid arthritis, skin tanning, acne and other skin disorders, neuroprotective and 25 cognitive and memory enhancement including the treatment of Alzheimer's disease.

Other conditions that can be treated with the MC receptor agonists of the invention include, but are not limited to, disuse deconditioning; organ damage such as 30 occurs in response to organ transplantation or ischemic injury such as that which can occur after reperfusion or stroke; adverse reactions associated with cancer chemotherapy; diseases such as atherosclerosis that are mediated by free radicals and nitric oxide action; bacterial

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endotoxic sepsis and related shock; adult respiratory distress syndrome; and autoimmune or other patho-immunogenic diseases or reactions such as allergic reactions or anaphylaxis, rheumatoid arthritis, inflammatory bowel 5 disease, ulcerative colitis, glomerulonephritis, systemic lupus erythematosus, transplant atherosclerosis and parasitic mediated immune dysfunctions such as Chagas' Disease.

Another aspect of the present invention provides a 10 method for the treatment or prevention of obesity or diabetes in a mammal which comprises administering to said mammal an effective amount of a compound of Formulas I-III. Compounds of the present invention also are useful as G-protein agonists.

15 Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

20 As used herein, the compounds of the present invention include the pharmaceutically acceptable derivatives thereof.

Definitions

25 As used herein, the terms "regulate" or "regulatory" mean to control by enhancing, limiting, restricting, restraining, modulating or moderating. Such regulation includes the pleiotropic, redundant, synergistic or antagonistic effects that occur due to the activity of 30 biological agents such as cytokines, which can affect a variety of biological functions directly or indirectly through cascade or biofeedback mechanisms.

The term "prevention" includes either preventing the onset of disorders altogether or

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delaying the onset of a pre-clinically evident stage of disorders in individuals. This includes prophylactic treatment of those at risk of developing a disease, such as a cancer, for example. "Prophylaxis" is another term for prevention.

A "pharmaceutically-acceptable derivative" denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

As used herein, "MCR4 agonist" and "MCR3 agonist" refers to a compound with affinity for MCR4 or MCR3, respectively, that results in measurable biological activity in cells, tissues, or organisms which contain MCR4 or MCR3.

As used herein, "MCR3" and "MCR4" mean the known MCR3 and MCR4 receptors, their splice variants, and undescribed receptors. MCR3 is described by Gantz et al., *supra* (human MCR3), Desarnaud et al., *supra* (mouse MCR3) and L. Reyfuss et al., *Proc. Natl. Acad. Sci. USA*, 90, 8856-8860 (1993) (rat MCR3). MCR4 receptors are described by Gantz et al., *supra* (human MCR4), J.D. Alvaro et al., *Mol. Pharmacol.*, 50, 583- 91 (1996) (rat MCR4) and Takeuchi, S. and Takahashi, S., *Gen- Comp-Endocrinol.*, 112(2), 220-31 (1998) (chicken MCR4).

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

"Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation,

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or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve an orgasm. The term "impotence" is oftentimes employed to
5 describe this condition.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within
10 other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl,
15 isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl (-CH₂-) and ethylenyl (-CH₂CH₂-).

20 The term "alkenyl" embraces linear or branched radicals of two to about twelve carbon atoms having at least one carbon-carbon double bond. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are
25 radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

30 The term "alkynyl" denotes linear or branched radicals having two to about twelve carbon atoms having at least one carbon-carbon triple bond. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are lower alkynyl radicals having two

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to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

5 The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo radicals as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an
10 iodo, bromo, chloro or fluoro atom within the radical.

Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl
15 radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl,
20 difluoropropyl, dichloroethyl and dichloropropyl.

"Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched
25 alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals
30 include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to

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about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Even more preferred are lower alkoxy 5 radicals having one to three carbon atoms.

Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms.

10 Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings 15 wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 to 3 substituents such as lower alkyl, hydroxyl, halo, 20 haloalkyl, nitro, cyano, alkoxy and lower alkylamino.

The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings 25 containing -O-O-, -O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino and lower alkylamino.

Examples of saturated heterocyclic radicals include 30 saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl];

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saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl,
5 dihydrofuryl and dihydrothiazolyl.

The term "heterocyclyl" also includes bridged heterocyclic groups, having 5-8 members. Examples of such radicals include 8-aza-bicyclo[3.2.1]octyl, 7-aza-bicyclo[2.2.1]heptyl, 5-aza-bicyclo[2.1.1]hexyl, and the like. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl,
15 pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom,
20 for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered
25 heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals:
30 unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g.,

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tetrazolo[1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., 5 benzothiazolyl, benzothiadiazolyl]. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include quinolyl, isoquinolyl, imidazolyl, pyridyl, thienyl, 10 thiazolyl, oxazolyl, furyl, and pyrazinyl. Other preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur, nitrogen and oxygen, selected from thienyl, furyl, pyrrolyl, indazolyl, pyrazolyl, oxazolyl, triazolyl, imidazolyl, 15 pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl and pyrazinyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $\text{-SO}_2\text{-}$.

20 The term "alkylsulfonyl" embraces sulfonyl radicals substituted with an alkyl radical. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylsulfonyl radicals having one to three carbon 25 atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, and ethylsulfonyl.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, $(-\text{SO}_2\text{NH}_2)$.

30 The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfonyl radicals are substituted with one or two alkylamino radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having alkyl portions of one to six carbon atoms.

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Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

5 The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-\text{CO}_2\text{H}$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes $-(\text{C}=\text{O})-$.

10 The term "aminocarbonyl" denotes an amide group of the formula $-\text{C}(=\text{O})\text{NH}_2$.

15 The term "alkoxycarbonyl" denotes an ester group, where a carbonyl radical is substituted with an alkoxy radical. More preferred are "lower alkoxycarbonyl" having lower alkoxy radicals as described above attached to a carbonyl radical.

20 The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals substituted with one or two alkyl radicals, respectively. More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

25 The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

30 The terms "heterocyclalkylenyl" and "heterocyclalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclalkylenyl radicals are "5- or 6-membered heterocyclalkylenyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heterocyclyl radical. Similarly, "heteroarylalkylenyl" and "heteroarylalkyl" embrace heteroaryl-substituted alkyl radicals. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions

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of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The terms "aralkyl" and "arylalkyl" embrace aryl-substituted alkyl radicals. Preferable aralkyl radicals are 5 "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" having alkyl portions of one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said 10 aralkyl may be additionally substituted, such as with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more 15 preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, ($\text{CH}_3\text{S}-$).

The term "alkylthioalkyl" embraces radicals containing a alkylthio radical, of one to ten carbon atoms, attached to 20 a linear or branched alkyl radical of one to about ten carbon atoms. Even more preferred are lower alkthioalkyl radicals, where each alkyl portion contains one to six carbon atoms. An example of "alkthioalkyl" is meththiomethyl (CH_3SCH_2-).

25 The term "alkoxyalkyl" embrace radicals containing an alkoxy radical, of one to about ten carbon atoms, attached to a linear or branched alkyl radical of one to about ten carbon atoms. More preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having alkyl portions each with one to 30 six carbon atoms. Examples of such radicals include methoxyethyl, ethoxymethyl, methoxymethyl, and the like. Even more preferred are lower alkoxyalkyl radicals where each alkyl portion has one to three carbon atoms.

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- The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" 5 radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.
- 10 The term "aminoalkylamino" embraces aminoalkyl radicals having one to about ten carbon atoms any one of which are substituted on an amino radical. More preferred aminoalkylamino radicals are "lower aminoalkylamino" radicals having one to six carbon atoms. Examples of such 15 radicals include aminomethylamino, aminoethylamino, aminopropylamino and aminobutylamino. Even more preferred are lower aminoalkylamino radicals having one to three carbon atoms.

20 The term "aminoalkoxy" embraces alkoxy radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkoxy radicals are "lower aminoalkoxy" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethoxy, and 25 aminopropoxy. Even more preferred are lower aminoalkoxy radicals having one to three carbon atoms.

20 The term "alkylcarbonylaminoalkyl" embraces aminoalkyl radicals which are substituted with an alkylcarbonyl radical. More preferred alkylcarbonylaminoalkyl radicals are 30 "lower alkylcarbonylaminoalkyl" radicals having alkyl portions each containing one to six carbon atoms. Examples of such radicals include methylcarbonylmethylamino, and the like. Even more preferred are lower alkylcarbonylaminoalkyl

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radicals having alkyl portions each containing one to three carbon atoms.

The term "alkylcarbonyl" denotes carbonyl groups which have been substituted with an alkyl radical. More preferred
5 are C₁-C₆-alkylcarbonyl radicals, such as methylcarbonyl, ethylcarbonyl and propylcarbonyl.

The term "alkoxyalkylcarbonyl" denotes alkylcarbonyl groups which have been substituted with one or more alkoxy radicals. More preferred are C₁-C₆-alkoxy-C₁-C₆-alkylcarbonyl
10 radicals, such as methoxymethylcarbonyl, and the like.

The term "arylcarbonyl" denotes carbonyl groups which have been substituted with aryl radicals, such as phenylcarbonyl. The arylcarbonyl radicals may be further substituted on the aryl ring portion of the radical.

15 The term "heteroarylcarbonyl" denotes carbonyl groups which have been substituted with a heteroaryl radical, such as thienylcarbonyl. The "heteroarylcarbonyl" radicals may be further substituted on the heteroaryl ring portion of the radical.

20 The terms "aralkylcarbonyl" and "arylalkylcarbonyl" denote carbonyl groups which have been substituted with aralkyl radicals. More preferred are phenyl-C₁-C₃-alkylcarbonyl radicals, such as benzylcarbonyl. The aralkylcarbonyl radicals may be further substituted on the
25 aryl ring portion.

The term "heterocyclalkylcarbonyl" denotes carbonyl groups which have been substituted with heterocyclalkyl radicals. More preferred are heterocyclyl-C₁-C₃-alkylcarbonyl radicals, such as thienylmethylcarbonyl, and
30 the like. The "heterocyclalkylcarbonyl" radicals may be further substituted on the heterocyclyl ring portion of the radical.

The term "heteroarylalkylcarbonyl" denotes carbonyl groups which have been substituted heteroarylalkyl radicals.

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More preferred are heteroaryl-C₁-C₃-alkylcarbonyl radicals, such as pyridylmethylcarbonyl, and the like. The "heteroarylalkylcarbonyl" radicals may be further substituted on the heteroaryl ring portion of the radical.

5 The term "cycloalkylcarbonyl" denotes carbonyl groups which have been substituted with cycloalkyl radicals, such as cyclopropylcarbonyl. More preferred contain C₃-C₆ cycloalkyl radicals. The "cycloalkylcarbonyl" radicals may be further substituted on the cycloalkyl ring portion of the radical.

10 The term "cycloalkylalkylcarbonyl" denotes carbonyl groups which have been substituted with cycloalkylalkyl radicals. More preferred are C₃-C₆ cycloalkyl-C₁-C₃-alkylcarbonyl radicals, such as cyclopentylmethylcarbonyl.

15 The cycloalkylalkylcarbonyl radicals may be further substituted on the aryl ring portion.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are substituted with one alkyl radical and with two alkyl radicals, respectively.

20 More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

25 The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl, such as N-

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methylaminomethyl, N,N-dimethylaminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkylamino" embraces alkylamino radicals substituted with alkylamino radicals. More preferred alkylaminoalkylamino radicals are "lower alkylaminoalkylamino" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkylamino radicals may be mono or dialkyl, such as N-methylaminomethylamino, N,N-dimethylaminoethylamino, N,N-diethylaminomethylamino or the like.

The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms, attached to a amino group. Even more preferred are lower alkylamino radicals having alkyl radicals of one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylaminomethyl, N,N-dimethylaminoethyl, N,N-diethylaminomethyl or the like.

The term "cycloalkylaminoalkyl" denotes aminoalkyl groups which have been substituted with one or two cycloalkyl radicals. More preferred are C₃-C₆-cycloalkylamino-C₁-C₃-alkyl radicals, such as N-cyclohexylmethylaminomethyl. The cycloalkylalkylaminoalkyl

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radicals may be further substituted on the cycloalkyl ring portion of the radical.

The term "cycloalkylalkylaminoalkyl" denotes aminoalkyl groups which have been substituted with one or 5 two cycloalkylalkyl radicals. More preferred are C₁-C₆-cycloalkyl-C₁-C₃-alkylamino-C₁-C₃-alkyl radicals, such as N-cyclohexylmethyldiaminomethyl. The cycloalkylalkylaminoalkyl radicals may be further substituted on the cycloalkyl ring portion.

10 The terms "aralkylamino" and "arylalkylamino" denote amino groups which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C₁-C₃-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

15 The term "heterocyclalkylamino" denotes amino groups which have been substituted with one or two heterocyclalkyl radicals. More preferred include heterocycl-C₁-C₃-alkylamino, such as N-thienylmethylamino, and the like. The "heterocyclalkylamino" radicals may be 20 further substituted on the heterocycl ring portion of the radical.

The term "heteroarylalkylamino" denotes amino groups which have been substituted with one or two heteroarylalkyl radicals. More preferred are heteroaryl-C₁-C₃-alkylamino, 25 such as N-thienylmethylamino, and the like. The "heteroarylalkylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted 30 with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "arylaminoalkyl" denotes aminoalkyl groups which have been substituted with one or two aryl radicals. More preferred are arylamino-C₁-C₃-alkyl radicals, such as

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N-phenylaminomethyl. The arylaminoalkyl radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylaminomethyl" denotes aminoalkyl groups which have been substituted with one or two 5 heteroaryl radicals. More preferred are heteroarylamo-C₁-C₃-alkyl radicals, such as N-thienylaminomethyl. The "heteroarylaminomethyl" radicals may be further substituted on the heteroaryl ring portion of the radical.

10 The terms "aralkylaminomethyl" and "arylalkylaminomethyl" denote aminoalkyl groups which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C₁-C₃-alkylamino-C₁-C₃-alkyl radicals, such as N-benzylaminomethyl. The aralkylaminomethyl radicals may be further substituted on the aryl ring portion.

15 The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio. The aryl portion may be further substituted.

20 The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C₁-C₃-alkylthio radicals. An example of "aralkylthio" is benzylthio. The aryl portion may be further substituted.

25 The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

30 The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above. The aryl portion may be further substituted.

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The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces heteroarylalkyl
5 radicals attached through an oxygen atom. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroarylalkyl radicals attached to lower alkoxy radical as described above.

10 The term "aryloxyalkyl" embraces radicals containing an aryloxy radical attached to a linear or branched alkyl radical of one to about ten carbon atoms. More preferred aryloxyalkyl radicals are "lower phenoxyalkyl" radicals having alkyl portions of one to six carbon atoms. Examples
15 of such radicals include phenoxyethyl, phenoxyethyl, and the like. Even more preferred are lower aryloxyalkyl radicals having alkyl portions of one to three carbon atoms.

The term "heteroaryloxyalkyl" embraces radicals containing an heteroaryloxy radical attached to a linear or
20 branched alkyl radical of one to about ten carbon atoms. More preferred heteroaryloxyalkyl radicals are "lower heteroaryloxyalkyl" radicals having alkyl portions of one to six carbon atoms. Examples of such radicals include pyridyloxyethyl, and the like. Even more preferred are lower
25 heteroaryloxyalkyl radicals having alkyl portions of one to three carbon atoms.

The term "heteroarylalkyloxyalkyl" embraces radicals containing an heteroarylalkyloxy radical attached to a linear or branched alkyl radical of one to about ten carbon
30 atoms. More preferred heteroarylalkyloxyalkyl radicals are "lower heteroarylalkyloxyalkyl" radicals having alkyl portions of one to six carbon atoms. Examples of such radicals include pyridylmethyloxyethyl, and the like. Even

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more preferred are lower heteroarylalkyloxyalkyl radicals having alkyl portions of one to three carbon atoms.

The term "aralkyloxyalkyl" embraces radicals containing an aralkyloxy radical attached to a linear or
5 branched alkyl radical of one to about ten carbon atoms. More preferred aralkyloxyalkyl radicals are "lower phenylalkyloxyalkyl" radicals having alkyl portions of one to six carbon atoms each. Examples of such radicals include benzylxyethyl, phenylethyloxymethyl, and the like. Even
10 more preferred are lower aralkyloxyalkyl radicals having alkyl portions of one to three carbon atoms each.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C₃-C₆ rings. More preferred compounds include, cyclopentyl, cyclopropyl,
15 and cyclohexyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The present invention preferably includes compounds
20 that are agonists of the melanocortin-4 receptor.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an obesity
25 mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-obesity medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent
30 disorders through antagonism of melanocortin receptor.

The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of Formulas I-III in association with a least one pharmaceutically-acceptable carrier, adjuvant or diluent.

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The present invention also comprises a method of treating obesity related disorders, in a subject, the method comprising treating the subject having or susceptible to such disorder with a therapeutically-effective amount of a 5 compound of Formulas I-III.

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they 10 can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic 15 agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a 20 regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate 25 capsules for each agent.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formula I may also be administered sequentially with known agents when a 30 combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I-III may be administered either prior to or after administration of the known agents.

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Specifically, the administration of compounds of the present invention may be in conjunction with additional antiobesity agents or appetite regulating agents, therapies known to those skilled in the art.

- 5 Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin-4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF
10 BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, P3 agonists, IVISH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and
15 noradrenaline re-uptake inhibitors, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA
20 (dopamine) agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR P
agonists.

Specifically such agents include leptin, topiramate, bupropion, dexamphetamine or amphetamine, fenfluramine,
25 dexfenfluramine or sibutramine, orlistat, mazindol or phentermine.

Furthermore, the present compounds may be administered in combination with one or more anti hypertensive agents. Examples of anti-hypertensive agents are P- blockers such as
30 alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine,

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nimodipine, diltiazem and verapamil, and α -blockers such as doxazosin, urapidil, prazosin and terazosin, insulin sensitizers including PPAR γ agonists [such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, 5 BRL49653 and the like)] and biguanides such as metformin and phenformin, insulin or insulin mimetics, sulfonylureas such as tolbutamide and glipizide, glucosidase inhibitors (such as acarbose), cholesterol lowering agents such as [HMG-CoA reductase inhibitors (lovastatin, simvastatin and 10 pravastatin, fluvastatin, atorvastatin, and other statins), sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl derivatives of a cross-linked dextran), nicotinyl alcohol nicotinic acid or a salt thereof, proliferator-activater receptor (α agonists such as 15 fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide, probucol, vitamin E, and thyromimetics] PPAR δ agonists, antiobesity compounds such as fenfluramine, 20 dexfenfluramine, phentermine, sibutramine, orlistat, or P3 adrenergic receptor agonists, feeding behavior modifying agents such as neuropeptide Y antagonists (e.g. neuropeptide Y5), PPAR α agonists by Glaxo, PPAR γ antagonists, serotonin 25 reuptake inhibitors such as fluoxetine and sertraline, growth hormone secretagogues such as MK-0677; and agents useful in the treatment of male and/or female sexual dysfunction which include phosphodiesterase V (PDE-V) inhibitors, such as sildenafil and IC-351; (α 2-adrenergic 30 receptor antagonists, such as phentolamine mesylate; and dopamine-receptor agonists, such as apomorphine. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

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The present invention comprises a process for the preparation of a compound of Formula I-III.

Compounds of the present invention can possess, in general, one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyletartaric, ditoluoyltartaric, and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of the invention with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of the invention can likewise be obtained by using active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Compounds of the present invention can possess, in general, tautomeric forms, which are included in the family of compounds in Formula I-III.

Also included in the family of compounds of Formula I-III are the pharmaceutically-acceptable salts thereof. The

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term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is

5 pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I-III may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and

10 phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic,

15 tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic,

20 sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric,

25 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I-III include metallic salts,

30 such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine,

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histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the
5 invention by reacting, for example, the appropriate acid or base with the compound of Formulas I-III.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and
10 iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible
15 products are thereby obtained.

Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid,
20 maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

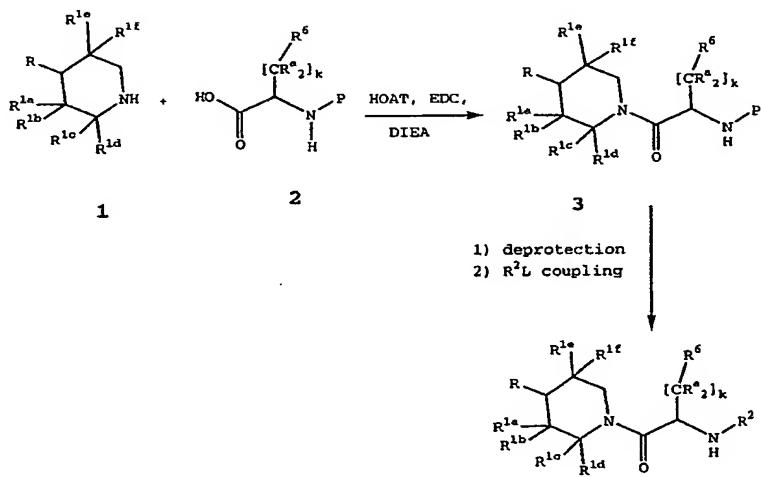
Additional examples of such salts can be found in
25 Berge et al., J. Pharm. Sci., 66, 1 (1977).

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GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the following procedures of Schemes 1-16, wherein the substituents are as defined for Formulas I-III, above, except where further noted.

Scheme 1



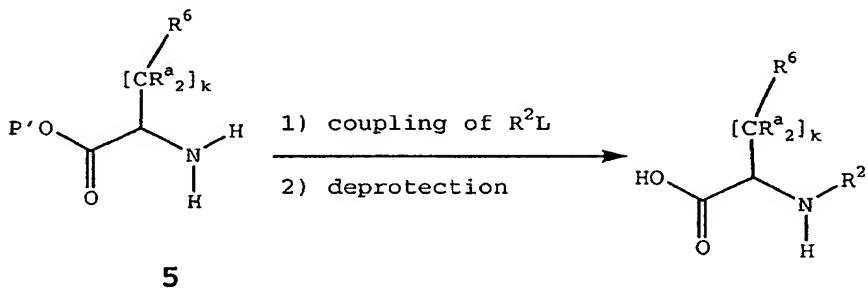
10

Compounds of Formula I may be prepared in a convergent manner as described in Scheme 1. Protected amino acids 2 (where P is a protecting group) are coupled with the substituted piperazine 1 using standard peptide coupling conditions, such as with HOAT EDC, and DIEA in a solvent, such as MeCl₂, and reacted at RT, to afford the protected piperazine amino acid 3. The protected amino acid derivatives 2 are commercially available or may be prepared by literature methods (R.M. Williams, Synthesis of Optically Active α -Amino Acids, Pergamon Press: Oxford, 1989). Similarly, substituted piperazines 1 are either commercially available, can be prepared via literature methods, or may be prepared following literature methods described for

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analogous compounds. Some of these methods are illustrated in the subsequent schemes. Removal of the protecting group P (CBZ, BOC, etc.) is accomplished using conventional methods, such as with a solution of 50% TFA and CH_2Cl_2 , to remove a Boc group, to yield the free amine. The free amine is treated with base, such as DIEA in a solvent, such as MeCl_2 . The reaction mixture is coupled with R^2L , such as a substituted acid using standard peptide coupling conditions, such as with HOAT, EDC, and DIEA in a solvent, at a temperature such as of about RT, to yield the desired compound 4.

Scheme 2



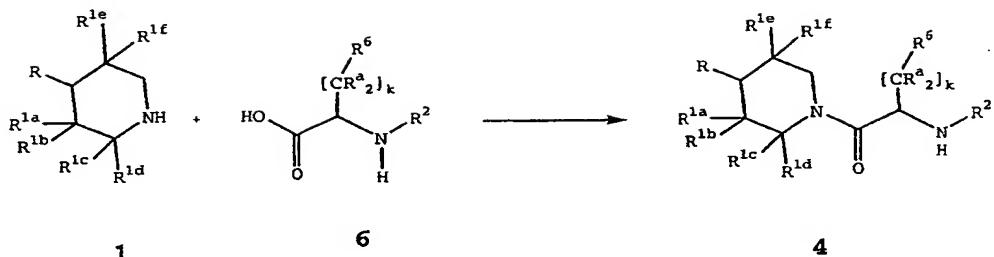
15

Amino acid ester intermediate 5, wherein P' is an acid protecting group including C₁₋₄ alkyl (such as methyl or ethyl), benzyl or allyl group, can be synthesized by well documented methods in the literature. Coupling of R²L (where L is a leaving group) and ester 5, such as with a substituted acid under standard peptide coupling conditions followed by removal of the ester group P' yields the intermediate 6.

25

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Scheme 3

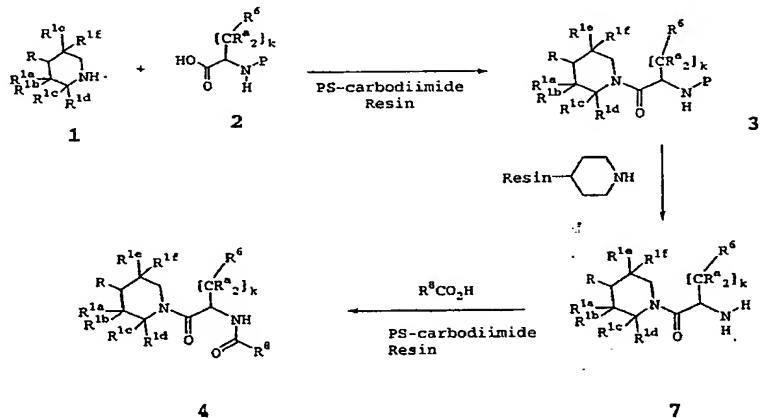


5

Compounds of Formula I may also be prepared in a convergent manner as described in Scheme 3. Compounds **4** are obtained by coupling intermediates **6** to piperidines **1** under standard peptide coupling reaction conditions.

10

Scheme 4



15

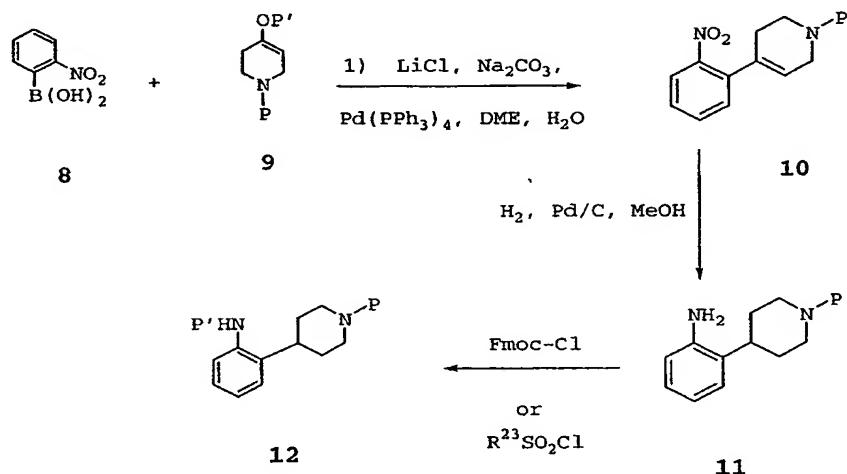
Chemical libraries can be made using variations of the above described chemistry to make compounds of Formula I, where R² is -C(=O)R⁸, as described in Scheme 4. Piperazine **1** is added to PS-carbodiimide resin, and an Fmoc protected amino acid. Excess piperazine **1** is scavenged, such as with 20 PS-isocyanate resin. The reaction mixture is filtered into

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scintillation vials containing DMAP and piperidine-4-carboxylic acid polyamine resin HL. PS-carbodiimide resin and R⁸CO₂H are added. The reactions are filtered and excess amine is scavenged, such as with PS-isocyanate resin. The 5 compounds are deprotected if needed to yield compounds 4. Other conditions and resins known to one skilled in the art can be used.

Scheme 5

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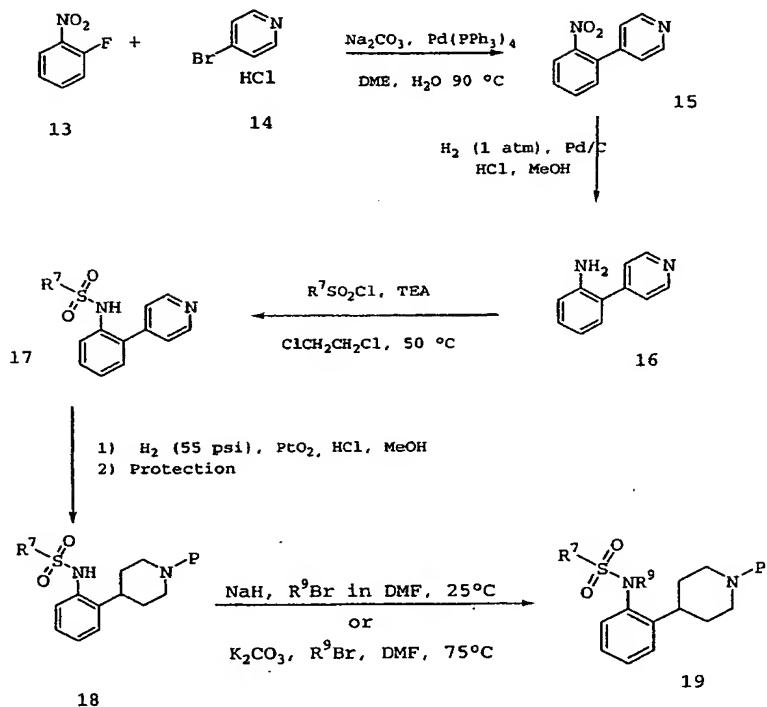
Substituted piperidines can be prepared such as by the method described in Scheme 5. Nitrophenyl boronic acids 8 15 are coupled with a protected tetrahydropyridines 9 such as with LiCl, and a catalyst, such as tetrakis(triphenylphosphine) palladium(0) in the presence of base, such as Na₂CO₃, at a temperature above RT, preferably above about 75°C, even more preferably at about 90°C, to 20 yield the nitrophenylpiperidine 10. The nitrophenylpiperidine 10 is converted to the amine 11, such as hydrogenation with H₂ and Pd/C. The amine 11 is protected (where treated with FMOC) or substituted to form the sulfonamide 12 (where treated with the sulfonyl

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chloride), at a temperature above RT, preferably at about 50°C.

Scheme 6

5



Substituted piperidines also can be prepared such as by the method described in Scheme 6. 2-Fluoronitrobenzene 10 13, is coupled with 4-bromopiperidine 14 such as with base, and a catalyst, such as Pd(PPh₃), to yield the nitrophenylpyridine 15. The nitro compound 15 is reduced to form the amine 16, such as with hydrogenation with H₂ in the presence of catalyst, such as Pd/C. The amine 16 is treated 15 with base, such as TEA (Aldrich) and a substituted sulfonyl chloride at a temperature above RT, preferably at about 50°C, to form the sulfonamide 17. The pyridyl sulfonamide 17 is converted to the piperidine such as by hydrogenation

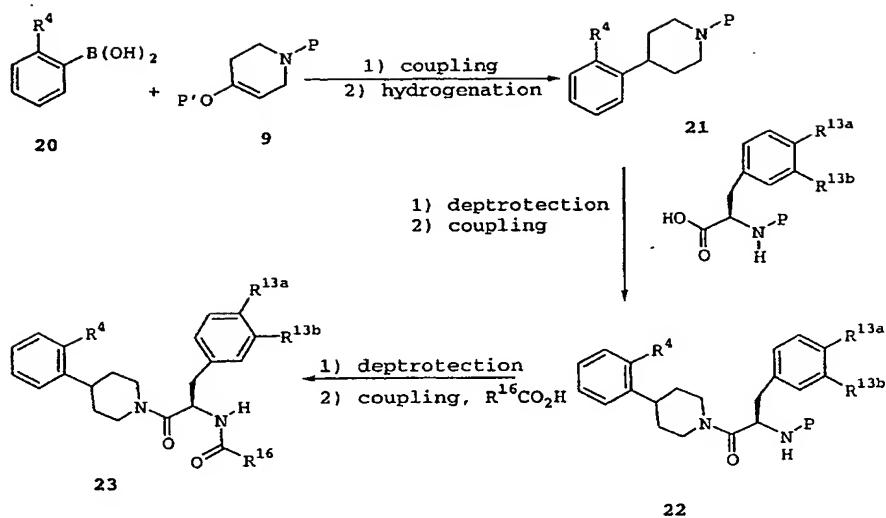
- 75 -

in the presence of catalyst, such as platinum(IV) oxide. The protected piperidine 18 is formed, such as with di-tert-butyl carbonate in the presence of base, at a temperature above RT, preferably at about 50°C. The substituted 5 sulfonamide 19 is formed by alkylation of 18, such as with NaH, at a temperature of about RT, or alternatively in the presence of base, such as K₂CO₃, a temperature above RT, preferably above about 50°C, even more preferably at about 75°C.

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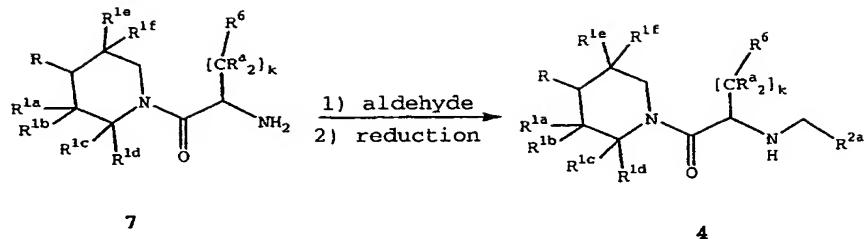
Scheme 7



5 Substituted piperidine derivatives also may be
 prepared by a process similar to that shown in Scheme 7.
 Phenylboronic acids **20** are coupled with tetrahydro-pyridines
 9 in the presence of base, such as Na_2CO_3 , and a catalyst,
 such as $Pd(PPh_3)_4$, followed by hydrogenation, such as with
 10 hydrogen in the presence of a catalyst, such as Pd on
 carbon, to yield the protected phenylpiperidines **21**. The
 phenylpiperidines **21** is deprotected, and coupled with the
 appropriate amino acid using traditional coupling chemistry
 to yield compound **22**. After further deprotection and
 15 coupling with R^2CO_2H , the piperidine derivatives **23** is
 formed with standard peptide chemistry.

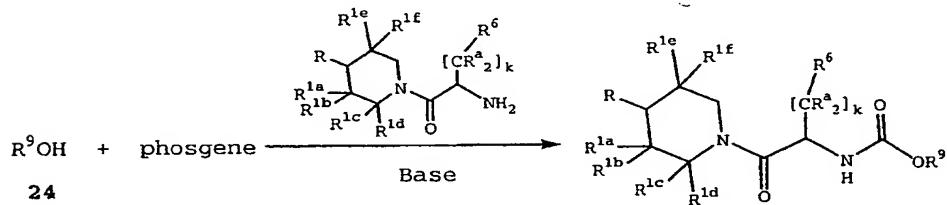
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Scheme 8



- 5 Compounds of Formula I, where R² is -CH₂R^{2a}, may be prepared in as described in Scheme 8. To a free amine 7 in a solvent, such as ClCH₂CH₂Cl, and base, such as DIEA, an aldehyde and reducing agent such as NaBH(OAc)₃ are added, to form the substituted amine 4, where R^{2a} is aryl, heterocyclyl or cycloalkyl. The reaction is preferably kept at about RT.
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Scheme 9



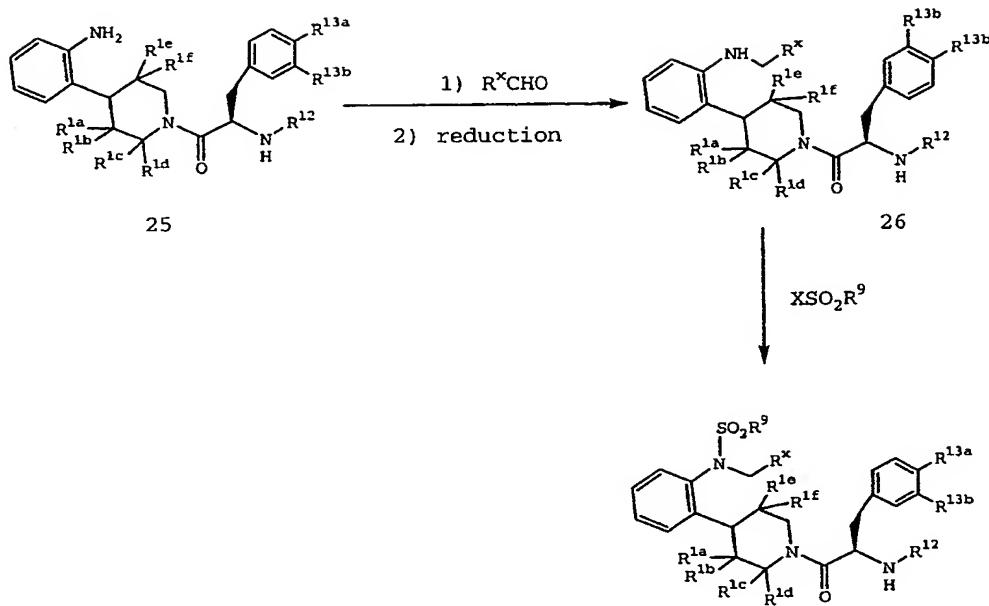
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- Compounds of Formula I, where R² is -C(=O)OR⁹, may also be prepared as described in Scheme 9. Alcohol 24 is converted to the anhydride, such as with phosgene and base, such as DIEA, at a temperature between -23°C and reflux, preferably at about 0°C and reflux, in a suitable solvent, such as CH₂Cl₂. To the mixture is added the piperazine derivative 7 and base to afford the carbamate 4. A similar
- 20

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procedure can be used for the reactions of amines to form the corresponding ureas.

Scheme 10

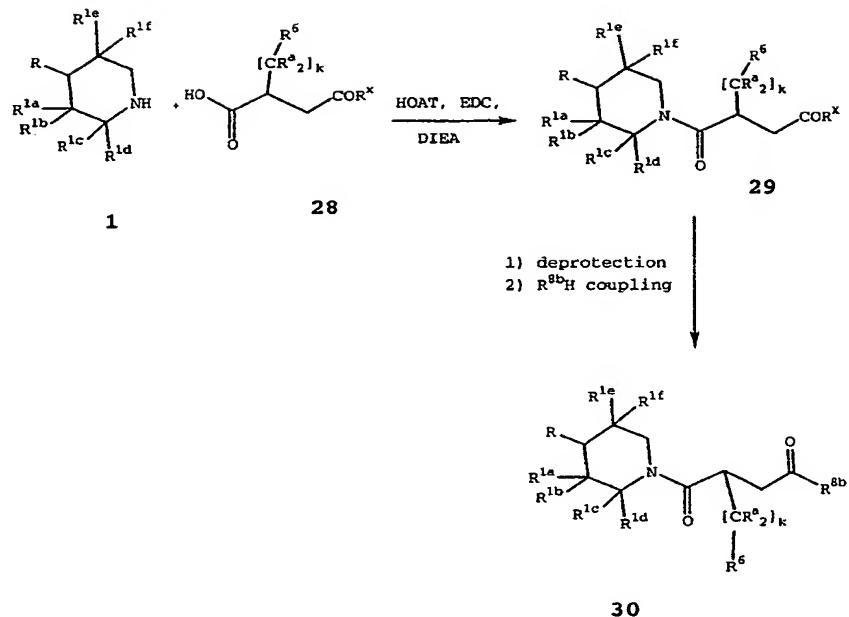


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Compounds of Formula I may also be prepared in a convergent manner as described in Scheme 10. Following the procedure for the synthesis of Scheme 9, the aniline 26 was prepared from the corresponding amine 25, aldehyde and reducing agent, such as NaBH(OAc)₃. The aniline 26 may be further substituted using, for example methylsulfonyl chloride, base such as pyridine, and DMAP (cat.), in a suitable solvent, such as ClCH₂CH₂Cl to yield the sulfonamide 27.

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Scheme 11



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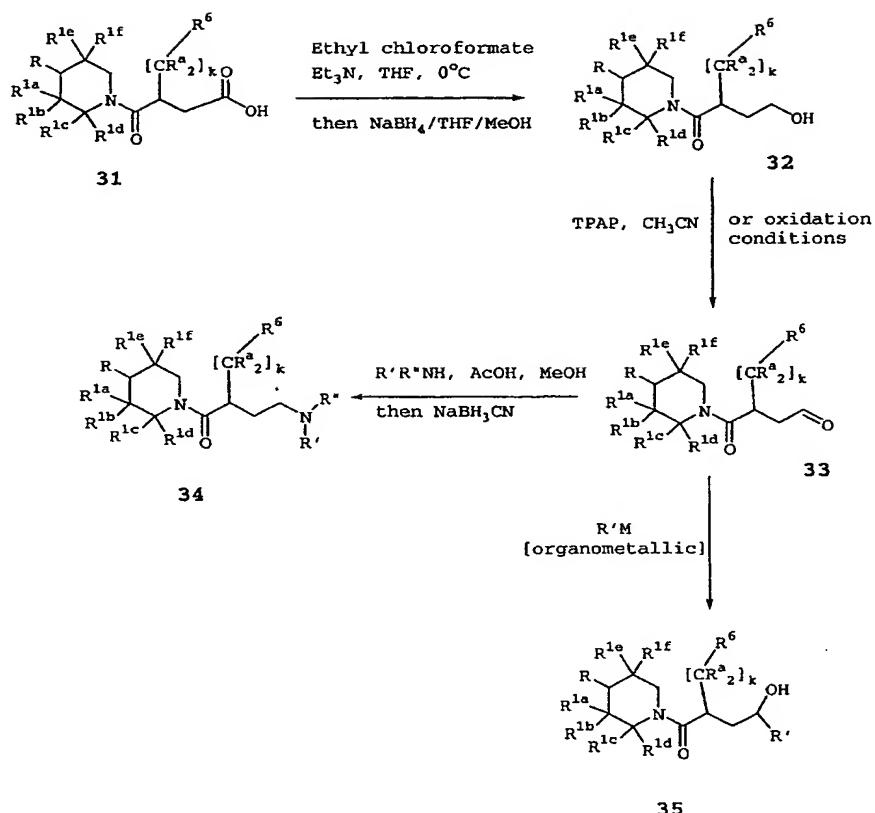
Compounds of Formula I, where R^2 is $-\text{COR}^8$ and Y is CH_2 may be prepared as described in Scheme 11. Piperidine 1 can be coupled with diacid 28 (where R^x is an acid protecting group, such as alkoxy, aryloxy, benzyloxy, and the like) to form the piperidinyl amide 29. The amide 29 is deprotected to form the free acid which can be coupled with appropriate reagents (where R^8b is capable of reacting with an acid, such as an optionally substituted amine) to form compounds 30. Such coupling can be with normal amino acid coupling reagents.

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~ 80 ~

Scheme 12



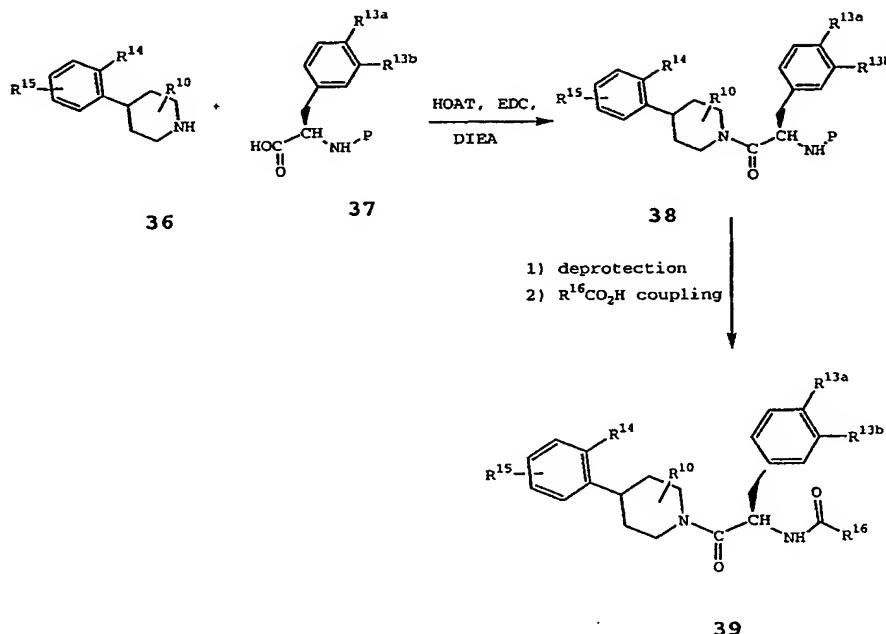
5 Alternatively, several types of compounds of Formula I, where R² is -COR⁸ and Y is CH₂ may be prepared as described in Scheme 12. The free acid 31 can be reduced to the alcohol 32, for example using a two step procedure that converts the acid 31 first to the mixed carbonate, such as 10 with ethyl chloroformate, then is reduced to the alcohol 32, such as with NaBH₄. The alcohol 32 can be converted to the aldehyde 33 (using reagents such as with Dess Martin reagent, TPAP or Swern oxidation) which can be further reacted with substituted amines, such as in the presence of 15 acetic acid, then reduced, such as with NaBH₃CN to form

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amines 34. Alternatively the aldehyde 33 can react with organometallic agents to form the alcohols 35.

Scheme 13

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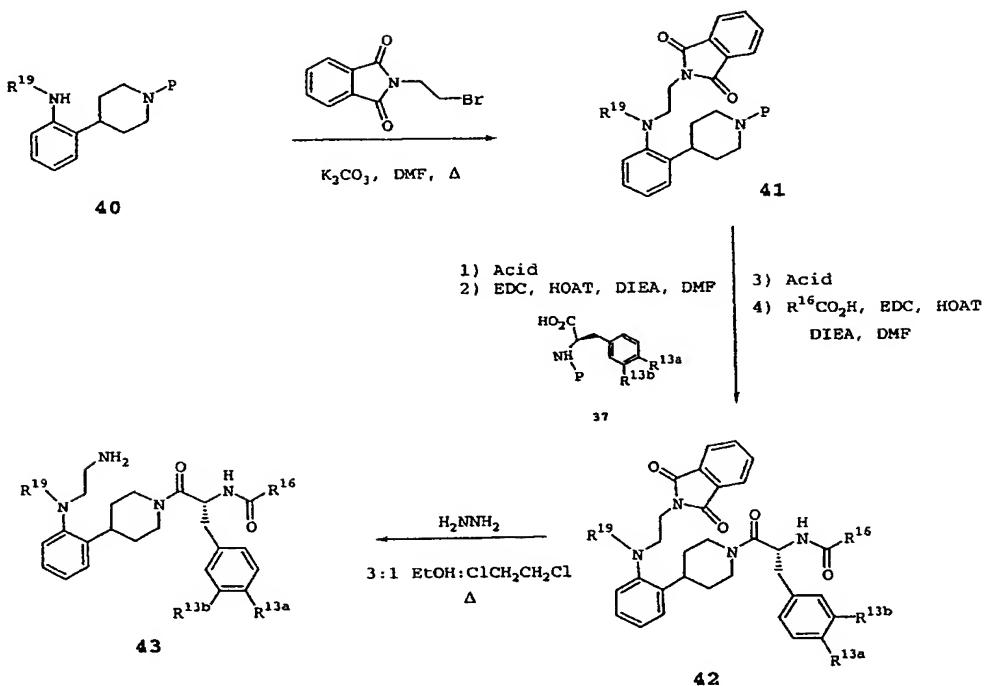
Compounds of Formula II may be prepared as described in Scheme 13. Protected D-phenylalanine derivatives 37
10 (where P is a protecting group) are coupled with the substituted phenyl piperazine 36 using standard peptide coupling conditions, such as with HOAT, EDC, and DIEA in a solvent, such as MeCl_2 , and reacted at RT, to afford the protected piperazine phenylalanine compounds 38. Removal of
15 the protecting group P (CBZ, BOC, Fmoc etc.) is accomplished using conventional methods, such as with a solution of 50% TFA and CH_2Cl_2 (to remove a Boc group), to yield the free amine. The free amine is treated with base, such as DIEA in a solvent, such as MeCl_2 . The reaction mixture is coupled
20 with a substituted acid, using standard peptide coupling

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conditions, such as with HOAT, EDC, and DIEA in a solvent, such as at a temperature of about RT, to yield the desired compound 39.

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Scheme 14



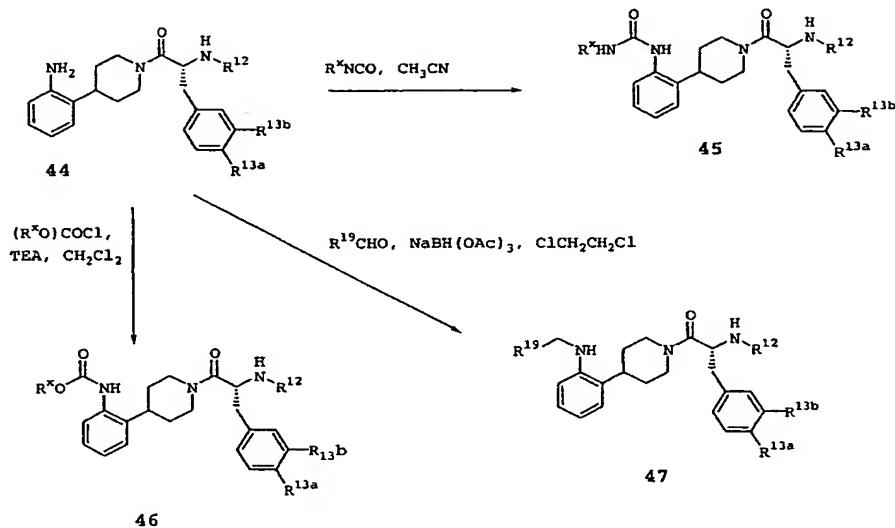
Compounds of Formula II, where R²⁰ is aminoalkyl, may
10 be prepared as described in Scheme 14. Aniline 40 is
coupled with a protected alkylamine, such as N-(2-
bromomethyl)phthalimide in the presence of base, to yield
the substituted amine 41. After treatment with acid, such
as HCl, at a temperature of about RT, coupling with normal
peptide conditions yields the protected piperidyl-
15 phenylalanine derivatives. Following acidification,
coupling with an acid yields the protected compound 42.
Deprotection, such as with hydrazine, at a temperature above

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RT, preferably at a temperature above 50°C, more preferably at about 60°C, yields the free amine **43**.

Scheme 15

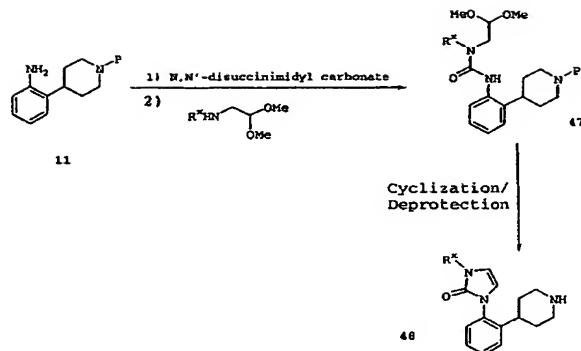
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Compounds of Formula II may be prepared as described in Scheme 15 starting with aniline **44**. The aniline **44** is reacted with an isocyanate to form ureas **45**. Alternatively, carbamic acid derivatives **46** can be prepared from treatment of the aniline **44** with acid halide esters, such as haloformates. Treatment of the aniline **44** with aldehydes in the presence of a reducing agent, such as NaB(OAc)_3 , provides the substituted amines **47**.

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Scheme 16



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Imidazolone substituted piperidines can be prepared by the method described in Scheme 16. The urea 47 is prepared from the aniline 11. *N,N'*-Disuccinimidyl carbonate is reacted with the aniline 11 (similar to the method described in WO01/44230), followed by treatment with a substituted 2,2-dimethoxyethylamine (similar to the method described in Wong et al., *Heterocycles*, 26, 3153-8 (1987)) to form the acetal 47. Similar to the method described in J. Org. Chem., 62, 2320-21 (1997), treatment with aqueous acid, such as TFA, affords the imidazolone 48. If the piperidine is protected with an acid labile protecting group, the acid also remove the protecting group.

The protected D-phenylalanine derivatives are commercially available or may be prepared by literature methods (R.M. Williams, *Synthesis of Optically Active α -Amino Acids*, Pergamon Press: Oxford, 1989). Similarly, substituted piperazines are either commercially available, can be prepared via literature methods, or may be prepared following literature methods described for analogous compounds. TIC derivatives can be prepared such as by methods described in WO00/74679. Piperazine derivatives can be prepared such as by methods described in WO95/34311.

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The starting compounds defined in Schemes 1-14 may also be present with functional groups in protected form if necessary and/or in the form of salts, provided a salt-forming group is present and the reaction in salt form is possible. If so desired, one compound of formula I can be converted into another compound of formula I or a N-oxide thereof; a compound of formula I can be converted into a salt; a salt of a compound of formula I can be converted into the free compound or another salt; and/or a mixture of isomeric compounds of formula I can be separated into the individual isomers.

N-Oxides can be obtained in a known matter by reacting a compound of formula I with hydrogen peroxide or a peracid, e.g. 3-chloroperoxy-benzoic acid, in an inert solvent, e.g. dichloromethane, at a temperature between about -10-35°C, such as about 0°C - RT.

If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a compound of formulas I-III, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily

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establish, which protecting groups are suitable with the reactions mentioned above and hereinafter.

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (Methods of organic chemistry), Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (Amino acids, peptides, proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of carbohydrates: monosaccharides and derivatives), Georg Thieme Verlag, Stuttgart 1974.

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned above under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known *per se*. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent. A salt with two acid molecules (for example a dihalogenide of a compound of formula I) may also

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be converted into a salt with one acid molecule per compound (for example a monohalogenide); this may be done by heating to a melt, or for example by heating as a solid under a high vacuum at elevated temperature, for example from about 130
5 to about 170°C, one molecule of the acid being expelled per molecule of a compound of formula I.

Salts can usually be converted to free compounds, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogen carbonates,
10 or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the
15 presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically cation exchangers, for example in the H⁺ form, depending on
20 the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from about -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at about -80°C to about 60°C, at room temperature, at about -20°C to about 40°C or at the boiling
25 point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

Salts may be present in all starting compounds and transients, if these contain salt-forming groups. Salts may
30 also be present during the reaction of such compounds, provided the reaction is not thereby disturbed.

In certain cases, typically in hydrogenation processes, it is possible to achieve stereoselective

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reactions, allowing for example easier recovery of individual isomers.

The solvents from which those can be selected which are suitable for the reaction in question include for 5 example water, esters, typically lower alkyl-lower alkanoates, e.g diethyl acetate, ethers, typically aliphatic ethers, e.g. diethylether, or cyclic ethers, e.g. THF, liquid aromatic hydrocarbons, typically benzene or toluene, alcohols, typically MeOH, EtOH or 1- or 10 2-propanol, nitriles, typically AcCN, halogenated hydrocarbons, typically CH₂Cl₂, acid amides, typically DMF, bases, typically heterocyclic nitrogen bases, e.g. pyridine, carboxylic acids, typically lower alkanecarboxylic acids, e.g. AcOH, carboxylic acid anhydrides, typically lower 15 alkane acid anhydrides, e.g. acetic anhydride, cyclic, linear, or branched hydrocarbons, typically cyclohexane, hexane, or isopentane, or mixtures of these solvents, e.g. aqueous solutions, unless otherwise stated in the description of the process. Such solvent mixtures may also 20 be used in processing, for example through chromatography or distribution.

The invention relates also to those forms of the process in which one starts from a compound obtainable at any stage as a transient and carries out the missing steps, 25 or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention and processes the said 30 compound *in situ*. In the preferred embodiment, one starts from those starting materials which lead to the compounds described above as preferred.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals.

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can include for example the solvent used for crystallization (present as solvates).

New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the 5 subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

Starting materials of the invention are known, are 10 commercially available, or can be synthesized in analogy to or according to methods that are known in the art.

The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures include 15 crystallization and normal-phase or reverse-phase chromatography.

In the preparation of starting materials, existing functional groups which do not participate in the reaction should, if necessary, be protected. Preferred protecting 20 groups, their introduction and their removal are described above or in the examples.

All remaining starting materials are known, capable of being prepared according to known processes, or commercially obtainable; in particular, they can be prepared using 25 processes as described in the examples.

The following examples contain detailed descriptions of the methods of preparation of compounds of Formula I. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic 30 Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention.

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Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures. Unless otherwise stated, reactions were run at room temperature.

10

The following abbreviations are used:

AcOH -	acetic acid
AlH ₃ -	aluminum hydride
Bn -	benzyl
15 Boc -	<i>tert</i> -(butoxycarbonyl)-
Boc-D-Phe-OH -	<i>N</i> - <i>tert</i> -(butoxycarbonyl)-D-phenylalanine
Boc-L-Tic-OH -	<i>N</i> - <i>tert</i> -(butoxycarbonyl)-L-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
20 Boc-p-Cl-D-Phe-OH -	<i>N</i> - <i>tert</i> -(butoxycarbonyl)- <i>para</i> -chloro-D-phenylalanine
Boc-D-3,4-diClPhe-OH -	<i>N</i> - <i>tert</i> -(butoxycarbonyl)-3,4-dichloro-D-phenylalanine
BOP-Cl -	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
25 CBZ-N-	Carbobenzyloxy
CH ₂ Cl ₂ -	dichloromethane, methylene chloride
ClCH ₂ CH ₂ Cl -	ethylene dichloride
CH ₃ CN -	acetonitrile
chxI -	cyclohexyl
30 Cond -	concentrated
cyp -	cyclopropyl
DIEA -	<i>N,N</i> -diisopropylethylamine
DMAP -	4-dimethylaminopyridine
DME -	ethylene glycol dimethylether

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	DMF -	dimethylformamide
	EDC -	1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide hydrochloride
	Et ₂ O -	diethyl ether
5	EtOAc -	ethyl acetate
	EtOH -	ethyl alcohol
	Fmoc -	N-(9-fluorenylmethoxycarbonyl)-
	g -	gram
	h -	hour
10	H ₂ -	hydrogen
	H ₂ O -	water
	H ₃ PO ₄ -	Phosphoric acid
	HCO ₂ NH ₄ -	ammonium formate
	HCl -	hydrochloric acid
15	HOAT -	1-hydroxy-7-azabenzotriazole
	HOBT -	1-hydroxybenzotriazole hydrate
	K ₂ CO ₃ -	potassium carbonate
	LDA -	lithium diisopropylamide
	LiOH -	lithium hydroxide
20	LiCl -	lithium chloride
	LiAlH ₄ -	lithium aluminum hydride
	mg -	milligram
	ml -	milliliter
	min -	minutes
25	MeOH -	methyl alcohol
	NaCl -	sodium chloride
	NaOH -	sodium hydroxide
	NaH -	sodium hydride
	Na ₂ CO ₃ -	sodium carbonate
30	NaHCO ₃ -	sodium bicarbonate
	NaBH ₃ CN -	sodium cyanoborohydride
	NaBH(OAc) ₃ -	sodium triacetoxyborohydride
	NaHMDS -	sodium bis(trimethylsilyl)amide
	NaH ₂ PO ₄ -	sodium phosphate monobasic

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	Na ₂ SO ₄ -	sodium sulfate
	N ₂ -	nitrogen
	NH ₃ -	ammonia
	NH ₄ Cl -	ammonium chloride
5	NH ₄ OAc -	ammonium acetate
	(NH ₄) ₂ SO ₄ -	ammonium sulfate
	Pd/C -	palladium on carbon
	phe -	phenylalanine
	pro -	proline
10	RT -	room temperature
	Satd -	saturated
	SiO ₂ -	silica
	SnCl ₂ •2H ₂ O -	stannous chloride, dihydrate
	soln -	solution
15	TEA -	triethylamine
	TFA -	trifluoroacetic acid
	THF -	tetrahydrofuran
	TIC -	tetrahydroisoquinoline carboxylic acid
	TicOH-	tetrahydro isoquinoline carboxylic acid
20	TPAP -	tetrapropyl ammonium perruthenate
	TLC -	thin layer chromatography

Preparative HPLC (TFA Buffer): Unless otherwise stated, compounds that were purified by preparative HPLC 25 using a TFA buffer were run on a YMC-ODS AM (150x20 mm, 5 micron particle size) column, with a flowrate of 20 mL/min. The eluant used was 10 to 100% CH₃CN in H₂O over 7 min then 3.5 min at 100% CH₃CN. Both solvents were buffered with 0.1% TFA.

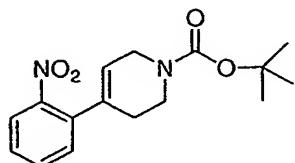
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Preparative HPLC (AcOH Buffer): The following method was used when AcOH was used as a buffer. YMC-ODS AM (150x20 mm, 5 micron particle size) column, with a flowrate of 20 mL/min. The eluant used was 10 to 100% CH₃CN in H₂O over 6

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min then 3.5 min at 100% CH₃CN. Both solvents were buffered with 0.1% AcOH.

Preparation A



5

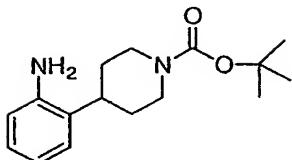
tert-Butyl 4-(2-nitrophenyl)-1,2,5,6-tetrahydropyridinecarboxylate.

To a 100 mL round-bottomed flask equipped with stirring was added 2-nitrophenyl boronic acid (Combi-Blocks Chemical Company) (210 mg, 1.3 mmol), LiCl (Aldrich) (168 mg, 4 mmol), tetrakis(triphenyl-phosphine)palladium (0) (Strem Chemical Company) (69 mg, 0.06 mmol) and *tert*-butyl 4-[(trifluoromethyl)-sulfonyloxy]-1,2,5,6-tetrahydropyridinecarboxylate [prepared by the method of Wustrow, D. J. and Wise, L. D., *Synthesis* 1991, 993-995, from *tert*-butyl-4-oxopiperidine-1-carboxylate (Aldrich), LDA (Aldrich) and *N*-phenyltrifluoromethanesulfonimide (Aldrich)] (397 mg, 1.2 mmol) in DME (5 mL). The reaction mixture was purged with N₂ and a 2 M soln of Na₂CO₃ (1.8 mL, 3.6 mmol) was introduced. After heating the mixture to 90°C for 3 h, the reaction was cooled to 25°C and diluted with EtOAc (15 mL). The organic layer was separated, washed with 10% Na₂CO₃, H₂O and satd NaCl and dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a dark yellow oil. The crude material was purified by column chromatography (3:1 hexane:EtOAc) to give the title compound as a white solid (240 mg). MS (ESI, pos. ion) *m/z*: 305 (M+1). Calc'd for C₁₆H₂₀N₂O₄: 304.34.

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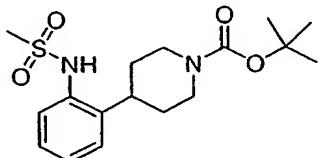
Preparation B



tert-Butyl 4-(2-aminophenyl)piperidinecarboxylate

To a pressure bottle was added *tert*-butyl 4-(2-nitrophenyl)-1,2,5,6-tetrahydropyridinecarboxylate (Preparation A) (145 mg, 0.48 mmol), 10% Pd/C (Aldrich) (51 mg) and 10 mL of a 1:1 mixture of MeOH:EtOH. The reaction mixture was hydrogenated at 50 psi overnight, then the crude mixture was filtered through Celite® (Aldrich) and concentrated *in vacuo* to afford the title compound as a colorless oil (128 mg, 97%). MS (ESI, pos. ion) *m/z*: 277 (M+1). Calc'd for C₁₆H₂₄N₂O₂: 276.37.

Preparation C



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tert-Butyl 4-(2-[(methylsulfonyl)amino]phenyl)piperidinecarboxylate.

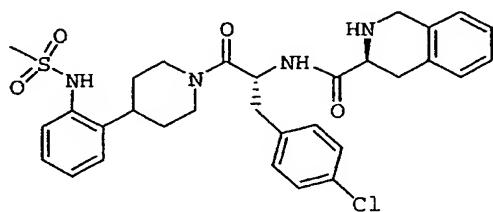
To a 100 mL round-bottomed flask was added *tert*-butyl 4-(2-aminophenyl)piperidinecarboxylate (Preparation B) (1.93 g, 7.2 mmol) and 1,2-dichloroethane (50 mL). The solution was magnetically stirred under a N₂ atmosphere, treated with pyridine (2.9 mL, 36 mmol) and methanesulfonyl chloride (Aldrich) (1.1 mL, 1.7 g, 14 mmol). The vessel was immersed in a 50°C oil bath for 6 h then cooled to 25°C. The solvent was removed *in vacuo*, and the residue was partitioned between EtOAc (200 mL) and 1 N HCl (100 mL). The organic layer was washed with satd NaHCO₃ (75 mL), satd NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated to give a

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foam. The foam was purified by silica gel chromatography (3:7 EtOAc:hexane) to provide the title compound as a white foam (2.1 g). MS (ESI, pos. ion) m/z : 355 (M+1); (ESI, neg. ion) m/z : 353 (M-1). Calc'd for $C_{17}H_{26}N_2O_4S$: 354.47.

5

Example 1



10 N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{(methylsulfonyl)amino]phenyl}-piperidyl]-2-oxoethyl}-((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide

Step (a) 4-(2-Nitrophenyl)-pyridine.

15 To a 1 L round-bottomed flask equipped with a reflux condenser was added 2-nitrobenzeneboronic acid (Lancaster) (10 g, 60 mmol), 4-bromopyridine hydrochloride (Fluka) (12 g, 60 mmol), Na_2CO_3 (25 g, 240 mmol), DME (300 mL) and H_2O (100 mL). The mixture was stirred magnetically, degassed *in vacuo* and purged with N_2 . The process was repeated five times then tetrakis(triphenylphosphine)-palladium (0) (Strem Chemicals) (3.5 g, 3.0 mmol) was added and the reaction mixture was stirred at reflux under a slight positive pressure of N_2 for 15 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (100 mL) and satd $NaCl$ (50 mL) diluted with H_2O (50 mL). The aqueous phase was further extracted with EtOAc (2 x 100 mL). The combined organic fractions were extracted with 1 N HCl (3 x 100 mL). The combined acidic extract was washed with EtOAc (100 mL), cooled in an ice bath and

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adjusted to pH 10 with 5 N NaOH. The aqueous solution was saturated with NaCl and extracted with EtOAc (3 x 100 mL). The combined EtOAc extracts were washed with satd NaCl (100 mL), dried over Na₂SO₄, filtered and concentrated to afford
5 a brown oil. Purification by silica gel chromatography (5:30:65, 1 M NH₃/MeOH-EtOAc-hexane) provided the title compound as a viscous, dark orange oil (6.0 g). MS (ESI, pos. ion) m/z: 201 (M+1). Calc'd for C₁₁H₈N₂O₂: 200.19.

10 **Step (b) 2-(4-Pyridyl)phenylamine.**

To a 500 mL round-bottomed flask was added a solution of 4-(2-nitrophenyl)-pyridine (Step a) (7.1 g, 36 mmol) in MeOH (300 mL). The solution was treated dropwise with concd HCl (6.7 mL, 84 mmol) and purged with N₂. Pd/C (10%, Aldrich)
15 (2.5 g) was added, H₂ was introduced and the suspension was magnetically stirred under atmospheric H₂ pressure for 15 h at 25°C. The suspension was purged with N₂, filtered through Celite® (Aldrich) (25 g) and the filter cake was washed with MeOH (400 mL). The filtrate was concentrated *in vacuo* to a yellow powder which was partitioned between EtOAc (200 mL) and 1 N NaOH (100 mL). The organic layer was washed with water (100 mL), satd NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the
20 title compound as a viscous yellow oil which solidified upon standing (6.0 g). MP 81-83°C. MS (ESI, pos. ion) m/z: 171 (M+1); (ESI, neg. ion) m/z: 169 (M-1). Calc'd for C₁₁H₁₀N₂: 170.21.

Step (c) (Methylsulfonyl)(2-(4-pyridyl)phenyl)amine.

30 A solution of 2-(4-pyridyl)phenylamine (Step b) (500 mg, 2.9 mmol) in 1,2-dichloroethane (35 mL) was stirred magnetically under N₂ in a 100 mL round-bottomed flask at 25°C. The solution was treated with TEA (Aldrich) (400 µL, 2.9 mmol) followed by methanesulfonyl chloride (Aldrich) (230 µL, 335

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mg, 2.9 mmol). The vessel was heated in a 50°C oil bath for 3 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between EtOAc (100 mL) and satd NaHCO₃ (50 mL). The organic layer was washed with satd NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a yellow oil. To the oil was added 5:25:75 1 M NH₃/MeOH:EtOAc:hexane (10 mL). A yellow precipitate formed which was collected by filtration and dried *in vacuo* at 40°C to afford the title compound as a 10 yellow solid (480 mg). MS (ESI, pos. ion) *m/z*: 249 (M+1); (ESI, neg. ion) *m/z*: 247 (M-1). Calc'd for C₁₂H₁₂N₂O₂S: 248.30.

Step (d) *tert*-Butyl 4-{2-[(methylsulfonyl)amino]phenyl}piperidine-carboxylate.

To a 250 mL Parr flask was added (methylsulfonyl)(2-(4-pyridyl)phenyl)amine (Step c) (480 mg, 1.9 mmol), MeOH (25 mL) and concd HCl (0.217 mL, 1.9 mmol). The flask was purged with N₂, then platinum (IV) oxide (Aldrich) (200 mg) 20 was added. The suspension was hydrogenated on a Parr shaker at 55 psi H₂ for 1 h, at which point the color of the methanolic solution changed from yellow to colorless. The reaction mixture was filtered through a bed of Celite® (Aldrich), and the filter cake was washed with MeOH (250 mL). The filtrate was concentrated *in vacuo* to 10 mL and EtOAc (40 mL) was added, resulting in precipitation of the compound. The precipitate was collected by filtration and dried *in vacuo* to afford a white solid (331 mg), which was used without further purification. The solid was suspended 25 in CH₂Cl₂ (10 mL) in a 50 mL round-bottomed flask and magnetically stirred at 25°C. To the suspension was added TEA (Aldrich) (0.32 mL, 2.28 mmol), followed by di-*tert*-butyl carbonate (Aldrich) (272 mg, 1.25 mmol). The mixture 30 was heated in a 50°C oil bath for 4 h. The mixture was

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removed from the oil bath and partitioned between CH₂Cl₂ (200 mL) and satd NaHCO₃ (20 mL). The organic layer was washed with satd NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated to give an oil. The oil was purified by 5 silica gel chromatography (1:4 EtOAc:hexane) to provide the title compound as a colorless oil (250 mg). MS (ESI, pos. ion) m/z: 355 (M+1); (ESI, neg. ion) m/z: 353 (M-1). Calc'd for C₁₇H₂₆N₂O₄S: 354.47.

10 **Step (e) 4-{2-[{Methylsulfonyl}amino]phenyl}-piperidine.**

To a 25 mL round-bottomed flask equipped with stirring was added tert-butyl 4-{2-[{methylsulfonyl}amino]phenyl}piperidine-carboxylate (Step d) (610 mg, 1.72 mmol) followed by a saturated soln of HCl in EtOAc (10 mL). 15 The reaction mixture was stirred at RT for 1 h and the title compound (HCl salt) was isolated by filtration as a white solid (460 mg). MS (ESI, pos. ion) m/z: 255 (M+1). Calc'd for C₁₂H₁₉ClN₂O₂S: 290.81.

20 **Step (f) N-[(1R)-1-{(4-Chlorophenyl)methyl}-2-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)-2-oxoethyl](tert-butoxy)carboxamide.**

To a round-bottomed flask equipped with stirring was added 4-{2-[{methylsulfonyl}amino]phenyl}piperidine (Step e) (400 mg, 1.38 mmol) and DMF (5 mL). The mixture was stirred for 25 5 min, then treated with N-Boc-p-Cl-D-PheOH (PepTech Corporation) (454 mg, 1.52 mmol), HOAT (Aldrich) (188 mg, 1.38 mmol), EDC (Aldrich) (529 mg, 2.76 mmol) and DIEA (Aldrich) (240 µL, 1.38 mmol) and stirred at RT for 2.5 h. 30 The reaction mixture was diluted with EtOAc (15 mL) and 10% Na₂CO₃ (20 mL) was added. The organic layer was separated, washed with 10% Na₂CO₃, H₂O and satd NaCl, dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the title

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compound as a white foam (655 mg). MS (ESI, pos. ion) *m/z*: 536 (M+1). Calc'd for C₂₆H₃₄ClN₃O₅S: 536.08.

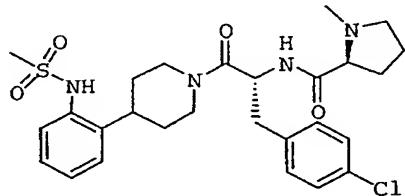
- Step (g) (2R)-2-Amino-3-(4-chlorophenyl)-1-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)propan-1-one.
The title compound was prepared according to the procedure described in Step (e) using N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)-2-oxoethyl](tert-butoxy)-carboxamide (Step f) (250 mg, 0.50 mmol) and a saturated soln of HCl in EtOAc (10 mL). The title compound (HCl salt) was isolated by filtration as a white solid (195 mg, 83%). MS (ESI, pos. ion) *m/z*: 473 (M+1). Calc'd for C₂₁H₂₇Cl₂N₃O₃S: 472.43.
- Step (h) tert-Butyl 3-{N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}-amino]phenyl}piperidyl)-2-oxoethyl]carbamoyl}(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.
The title compound was prepared according to the procedure described in Step (f) using (2R)-2-amino-3-(4-chlorophenyl)-1-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)propan-1-one (Step g) (325 mg, 0.74 mmol), Boc-L-TicOH (Bachem Company) (225 mg, 0.81 mmol), HOAT (Aldrich) (101 mg, 0.74 mmol), EDC (Aldrich) (284 mg, 1.48 mmol) and DIEA (Aldrich) (129 µL, 0.74 mmol) in DMF (5 mL). The title compound was obtained after purification by silica gel chromatography (1:2 hexane:EtOAc) as a white solid (310 mg). MS (ESI, pos. ion) *m/z*: 695 (M+1). Calc'd for C₃₆H₄₃ClN₄O₆S: 695.27.
- Step (i) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide.
The title compound was prepared according to the procedure described in (Step e) using tert-butyl 3-{N-[(1R)-1-[(4-

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chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)-
amino]phenylpiperidyl}2-oxoethyl)carbamoyl) (3S)-1,2,3,4-
tetrahydroisoquinoline-2-carboxylate (Step h) (310 mg, 0.45
mmol) and a saturated soln of HCl in EtOAc (10 mL). The
5 title compound was isolated by filtration and purified by
reverse phase preparative HPLC [LUNA C₁₈; 5 µm, 250 x 20 mm;
20% to 100% CH₃CN/H₂O (95:5, 20 mM NH₄OAc, pH 4.5) in H₂O (20
mM NH₄OAc, pH 4.5) over 6 min, then 100% CH₃CN/H₂O (95:5, 20
mM NH₄OAc, pH 4.5) for 5 min; 20 mL/min] to provide the
10 acetate salt as a white solid (145 mg, 47%). MS (ESI, pos.
ion) m/z: 595 (M+1). Calc'd for C₃₁H₃₅N₄O₄SCl: 594.21. Anal.
Calcd for C₃₁H₃₅N₄O₄SCl·C₂H₄O₂·1.5H₂O: C, 58.10; H, 6.21; N,
8.21; Cl, 5.20. Found: C, 58.30; H, 6.12; N, 8.20; Cl,
5.25.

15

Example 2



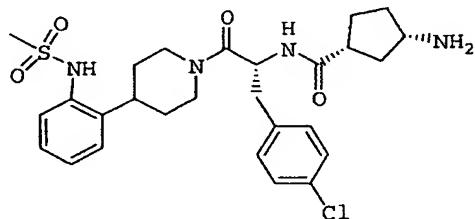
20 **N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{(methylsulfonyl)amino}phenyl)piperidyl]-2-oxoethyl]((2S)-1-methylpyrrolidin-2-yl)carboxamide**

The title compound was prepared according to the
25 procedure described in Example 1, Step (f) using (2R)-2-
amino-3-(4-chlorophenyl)-1-(4-{2-[(methylsulfonyl)-
amino]phenyl}piperidyl)propan-1-one (Example 1, Step g) (210
mg, 0.48 mmol), N-methyl S-proline (Bachem Company) (68 mg,
0.53 mmol), HOAT (Aldrich) (65 mg, 0.48 mmol), EDC (Aldrich)
30 (184 mg, 0.96 mmol) and DIEA (Aldrich) (84 µL, 0.48 mmol).

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Purification by reverse phase preparative HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound as a colorless oil (120 mg). MS 5 (ESI, pos. ion) *m/z*: 547 (M+1). Calc'd for C₂₇H₃₅ClN₄O₄S: 546.21.

Example 3



10

N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((3S,1R)-3-aminocyclopentyl)carboxamide

15

Step (a) N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]-{(3S,1R)-3-[(tert-butoxy)carbonylamino]-cyclopentyl}-carboxamide.

20 The title compound was prepared according to the procedure described in Example 1, Step (f) using (2R)-2-amino-3-(4-chlorophenyl)-1-(4-{2-[(methylsulfonyl)-amino]phenyl}piperidyl)propan-1-one (Example 1, Step g) (471 mg, 1.0 mmol), DIEA (Aldrich) (0.20 mL, 1.0 mmol), (+)-(1R, 3S)-25 N-Boc-aminocyclopentane-3-carboxylic acid (PepTech Corporation) (344 mg, 1.5 mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich) (544, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (421 mg). MS

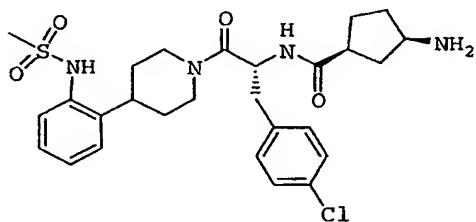
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(ESI, pos. ion) m/z : 647 (M+1); MS (ESI, neg. ion) m/z : 645 (M-1). Calc'd for $C_{32}H_{43}ClN_4O_6S$: 647.23

Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((3S,1R)-3-aminocyclopentyl)carboxamide.

To a 50 mL round-bottomed flask was added N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((3S,1R)-3-[(*tert*-butoxy)carbonylamino]-cyclopentyl)-carboxamide (Step a) (323 mg, 0.5 mmol) followed by a 50% soln of TFA in CH_2Cl_2 (20 mL). After stirring for 2 h, the solvent was removed in vacuo. Purification by preparative HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) over 30 min, then 100% CH_3CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (145 mg). MS (ESI, pos. ion) m/z : 547 (M+1); (ESI, neg. ion) 545 (M-1). Calc'd for $C_{27}H_{35}ClN_4O_4S$: 546.21. Anal. Calcd for $C_{27}H_{35}ClN_4O_4S \cdot 1.2C_2HF_3O_2$: C, 51.63; H, 5.49; N, 8.19. Found: C, 51.69; H, 5.49; N, 8.14.

Example 4



25

N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((1S,3R)-3-aminocyclopentyl)carboxamide

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Step (a) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl]-{(1S,3R)-3-[(tert-butoxy)carbonylamino]-cyclopentyl}-carboxamide.

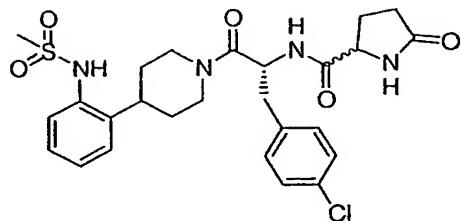
5 The title compound was prepared according to the procedure described in Example 1, Step (f) using (2R)-2-amino-3-(4-chlorophenyl)-1-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)propan-1-one (Example 1, Step g) (471 mg, 1.0 mmol), DIEA (Aldrich) (0.20 mL, 1.0 mmol), (-)-(1S,10 3R)-N-Boc-aminocyclopentane-3-carboxylic acid (PepTech Corporation) (344 mg, 1.5 mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (402 mg). MS 15 (ESI, pos. ion) m/z : 647 (M+1); MS (ESI, neg. ion) m/z : 645 (M-1). Calc'd for $C_{32}H_{43}ClN_4O_6S$: 647.23.

Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl][(1S,3R)-3-aminocyclopentyl]carboxamide.

20 The title compound was prepared according to the procedure described in Example 3 Step (b) from N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl][(1S,3R)-3-[(tert-butoxy)carbonylamino]-cyclopentyl}-carboxamide (Step a) (323 mg, 0.5 mmol) and a 50% soln of TFA in CH_2Cl_2 (20 mL). Purification by preparative HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) over 30 min, then 100% CH_3CN (0.1% TFA) for 2 min] provided the 25 title compound (TFA salt) as a white foam (113 mg). MS (ESI, pos. ion) m/z : 547 (M+1); (ESI, neg. ion) m/z : 545 (M-1). Calc'd for $C_{27}H_{35}ClN_4O_4S$: 546.21.

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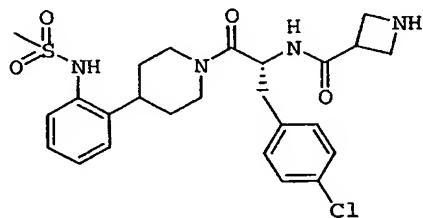
Example 5



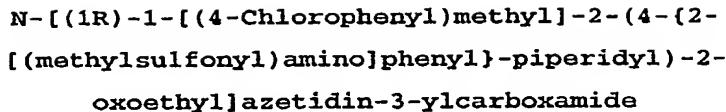
5 **N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]-5-
oxopyrrolidin-2-yl]carboxamide**

The title compound was prepared according to the
10 procedure described in Example 1, Step (f) using (2R)-2-
amino-3-(4-chlorophenyl)-1-(4-{2-[(methylsulfonyl)-amino]
phenyl}piperidyl)propan-1-one (Example 1, Step g) (118 mg,
0.25 mmol), DIEA (Aldrich) (0.05 mL, 0.25 mmol), DL-
pyroglutamic acid (Aldrich) (344 mg, 0.5 mmol), HOAT
15 (Aldrich) (68.2 mg, 0.5 mmol) and EDC (Aldrich) (95.8 mg,
0.5 mmol) in DMF (3 mL). Purification by silica gel
chromatography (100% EtOAc) provided the title compound as a
colorless film (82 mg). MS (ESI, pos. ion) *m/z*: 547 (M+1);
(ESI, neg. ion) *m/z*: 545 (M-1). Calc'd for C₂₆H₃₁ClN₄O₅S:
20 546.17.

Example 6



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5 **Step (a) tert-Butyl 3-{N-[(1R)-1-[(4-chlorophenyl)-methyl]-2-(4-{2-[methylsulfonyl]-amino}phenyl)-piperidyl]-2-oxoethyl}-carbamoyl}azetidinecarboxylate.**

The title compound was prepared according to the procedure described in Example 1, Step (f) using (2R)-2-amino-3-(4-chlorophenyl)-1-(4-{2-[methylsulfonyl]-amino}phenyl)piperidyl propan-1-one (Example 1, Step g) (471 mg, 1.0 mmol), DIEA (Aldrich) (0.20 mL, 1.0 mmol), Boc-azetidine-3-carboxylic acid (PepTech Corporation) (344 mg, 1.5 mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (1:10 MeOH:EtOAc) provided the title compound as a white foam (422 mg). MS (ESI, pos. ion) m/z: 619 (M+1); (ESI, neg. ion) m/z: 617 (M-1). Calc'd for C₃₀H₃₉ClN₄O₆S: 619.17.

20

Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[methylsulfonyl]amino}phenyl)-piperidyl]-2-oxoethyl]azetidin-3-ylcarboxamide

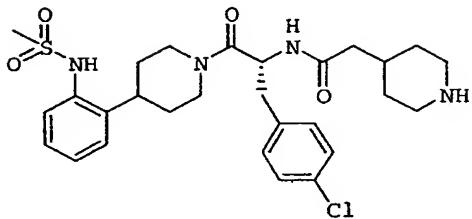
The title compound was prepared according to the procedure described in Example 3 (Step b) from tert-butyl 3-{N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[methylsulfonyl]-amino}phenyl)-piperidyl]-2-oxoethyl}-carbamoyl}azetidinecarboxylate (Step a) (309 mg, 0.5 mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by preparative reverse phase HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (205 mg). MS (ESI, pos. ion) m/z: 519 (M+1); (ESI, neg. ion) m/z: 517 (M-1). Calc'd for

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$C_{25}H_{31}ClN_4O_4S$: 518.18. Anal. Calcd for $C_{25}H_{31}ClN_4O_4S \cdot 1.4C_2HF_3O_2$: C, 49.20; H, 4.81; N, 8.26. Found: C, 49.31; H, 4.91; N, 8.25.

5

Example 7



10

N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{(methylsulfonyl)amino}phenyl)piperidyl]-2-oxoethyl]-2-(4-piperidyl)acetamide

Step (a) tert-Butyl 4-({N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{(methylsulfonyl)amino}phenyl)piperidyl]-2-oxoethyl}carbamoyl)methyl)piperidinecarboxylate.

15 The title compound was prepared according to the procedure described in Example 1, Step (f) using (2R)-2-amino-3-(4-chlorophenyl)-1-(4-{2-[(methylsulfonyl)amino]phenyl}piperidyl)propan-1-one (Example 1, Step g) (471 mg, 1.0 mmol), DIEA (Aldrich) (0.20 mL, 1.0 mmol), N-Boc-4-piperidineacetic acid (AstaTech, Inc.) (365 mg, 1.5 mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (441 mg). MS (ESI, pos. ion) m/z : 661 (M+1); (ESI, neg. ion) m/z : 590 (M-1). Calc'd for $C_{33}H_{45}ClN_4O_6S$:

20 661.25.

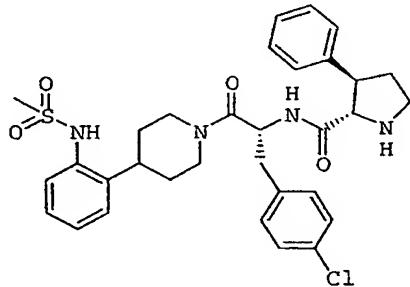
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Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)-2-oxoethyl]-2-(4-piperidyl)acetamide.

The title compound was prepared according to the procedure described in Example 3, Step (b) from *tert*-butyl 4-((N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}piperidyl)-2-oxoethyl]-carbamoyl)methyl)-piperidinecarboxylate (Step a) (330 mg, 0.5 mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by preparative reverse phase HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (242 mg). MS (ESI, pos. ion) *m/z*: 561 (M+1); (ESI, neg. ion) *m/z*: 559 (M-1). Calc'd for C₂₈H₃₇ClN₄O₄S: 560.22. Anal. Calcd for C₂₈H₃₇ClN₄O₄S·1.6C₂HF₃O₂: C, 50.40; H, 5.23; N, 7.53. Found: C, 50.54; H, 5.53; N, 7.75.

Example 8

20



25 N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl]((2S,3R)-3-phenylpyrrolidin-2-yl)carboxamide

Step (a) Fluoren-9-ylmethyl 2-(N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]

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phenyl)piperidyl)-2-oxoethyl]carbamoyl}(2S,3R)-3-phenylpyrrolidine carboxylate.

The title compound was prepared according to the procedure described in Example 1, Step (f) using (2R)-2-amino-3-(4-

5 chlorophenyl)-1-(4-{2-[{methylsulfonyl}-
amino]phenyl)piperidyl}propan-1-one (Example 1, Step g) (471
mg, 1.0 mmol), DIEA (Aldrich) (0.20 mL, 1.0 mmol), Fmoc-L-
transPro(3-Ph) (RSP Amino Acid Analogues, Inc.) (620 mg, 1.5
mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich)
10 (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica
gel chromatography (100% EtOAc) provided the title compound
as a white foam (554 mg). MS (ESI, pos. ion) 831 (M+1);
(ESI, neg. ion) m/z: 829 (M-1). Calc'd for C₄₇H₄₇ClN₄O₆S:
831.42.

15

Step (b) N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl](2S,3R)-3-phenylpyrrolidin-2-yl]carboxamide.

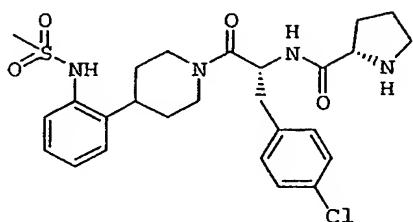
The title compound was prepared according to the procedure

20 of Sheppeck, J. E., et al. (*Tetrahedron Lett.* 2000, 41,
5329-5333) using fluoren-9-ylmethyl 2-{N-[(1R)-1-[(4-
chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]
phenyl)piperidyl)-2-oxoethyl]carbamoyl}(2S,3R)-3-
phenylpyrrolidine carboxylate (Step a) (415 mg, 0.5 mmol),
25 THF (10 mL), n-octanethiol (Aldrich) (876 mg, 6 mmol) and
1,8-diazabicyclo[5.4.0]undec-7-ene (Aldrich) (5 mg, 0.03
mmol). The reaction mixture was stirred for 5 h at 25°C and
the organic solvent was removed *in vacuo*. To the residue
30 was added Et₂O (20 mL) resulting in precipitation of the
compound. The precipitate was collected by filtration and
washed with hexane to provide a yellow solid. Purification
by preparative reverse phase HPLC [Phenomenex; 5 µm 250 x
21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over
30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the

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title compound (TFA salt) as a white foam (187 mg). MS (ESI, pos. ion) m/z : 609 (M+1); (ESI, neg. ion) m/z : 607 (M-1). Calc'd for $C_{32}H_{37}ClN_4O_4S$: 608.22. Anal. Calcd for $C_{32}H_{37}ClN_4O_4S \cdot 1.4C_2HF_3O_2$: C, 54.37; H, 5.03; N, 7.29. Found: 5 C, 54.26; H, 5.19; N, 7.41.

Example 9



10

N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(2-[(methylsulfonyl)amino]phenyl)-piperidyl]-2-oxoethyl]((2S)pyrrolidin-2-yl)carboxamide

15 Step (a) **tert-Butyl 2-{N-[(1R)-1-[(4-chlorophenyl)-methyl]-2-(4-{2-[(methylsulfonyl)-amino]-phenyl}-piperidyl)-2-oxoethyl]carbamoyl}-(2S)pyrrolidinecarboxylate.**

The title compound was prepared according to the procedure described in Example 1, Step (f) using (2R)-2-amino-3-(4-chlorophenyl)-1-(4-{2-[(methylsulfonyl)-amino]phenyl}piperidyl)propan-1-one (Example 1, Step g) (471 mg, 1.0 mmol), DIEA (Aldrich) (0.20 mL, 1.0 mmol), Boc-ProOH (Fisher Scientific) (323 mg, 1.5 mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (428 mg). MS (ESI, pos. ion) m/z : 633 (M+1); (ESI, neg. ion) m/z : 631 (M-1). Calc'd for $C_{31}H_{41}ClN_4O_6S$: 633.20.

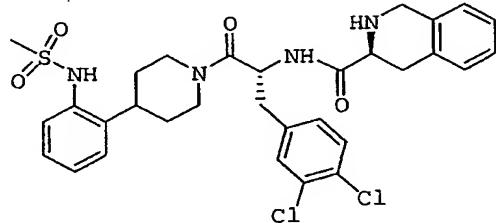
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Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}amino]phenyl}-piperidyl)-2-oxoethyl]((2S)pyrrolidin-2-yl)carboxamide.

The title compound was prepared according to the procedure described in Example 3, Step (b) from *tert*-butyl 2-{N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}-amino]phenyl}-piperidyl)-2-oxoethyl]carbamoyl}(2S)pyrrolidinecarboxylate (Step a) (315 mg, 0.5 mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by preparative reverse phase HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (101 mg). MS (ESI, pos. ion) *m/z*: 533 (M+1); (ESI, neg. ion) *m/z*: 531 (M-1). Calc'd for C₂₆H₃₃ClN₄O₄S: 532.19. Anal. Calcd for C₂₆H₃₃ClN₄O₄S·1.2C₂HF₃O₂: C, 50.92; H, 5.15; N, 8.36. Found: C, 50.82; H, 5.32; N, 8.38.

Example 10

20



((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-[(1R)-1-[(3,4-dichlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}-amino]phenyl}-piperidyl)-2-oxoethyl]carboxamide
25

Step (a) N-[(1R)-1-[(3,4-Dichlorophenyl)methyl]-2-(4-{2-[{methylsulfonyl}-amino]phenyl}-piperidyl)-2-oxoethyl](tert-butoxy)carboxamide

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The title compound was prepared according to the procedure described in Example 1 Step (f) using 4-{2-[(methylsulfonyl)amino]phenyl}piperidine (Example 1 Step e) (0.9 g, 3.1 mmol), Boc-D-3,4-diCl-Phe-OH (Advanced ChemTech) (1.04 g, 3.1 mmol), EDC (Advanced ChemTech) (0.89 g, 4.65 mmol), HOAT (Aldrich) (0.42 g, 3.1 mmol) and TEA (Aldrich) (0.65 mL, 4.65 mmol) in DMF (10 mL). Purification by silica gel chromatography (1:1 EtOAc:hexane then 100% EtOAc) provided the title compound as a pale yellow solid (0.6 g).

10 MS (ESI, pos. ion) *m/z*: 570 (M+1); MS (ESI, neg. ion) *m/z*: 568 (M-1). Calc'd for C₂₆H₃₃Cl₂N₃O₅S: 570.53.

Step (b) *tert*-Butyl (3*S*)-3-{N-[(1*R*)-1-[(3,4-dichlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

To a round-bottomed flask equipped with stirring was added N-[(1*R*)-1-[(3,4-dichlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]-(*tert*-butoxy)carboxamide (Step a) (0.455 g, 0.8 mmol) and a saturated soln of anhydrous HCl in EtOAc (20 mL). The reaction mixture was stirred at RT for 1 h then concentrated *in vacuo* to provide a solid. The solid was dissolved in DMF (10 mL), stirred at 0°C and treated with Boc-L-TicOH (Advanced ChemTech) (0.25 g, 0.9 mmol), HOAT (Aldrich) (0.122 g, 0.9 mmol), TEA (Aldrich) (0.188 mL, 1.35 mmol) then EDC (Advanced ChemTech) (0.26 g, 1.35 mmol). The reaction mixture was warmed to RT over 2 h, then stirred at RT for 12 h. The reaction mixture was diluted with EtOAc (70 mL), washed with satd NaHCO₃ (50 mL), satd NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (1:1 EtOAc:hexane then 100% EtOAc) provided the title compound as a white foam

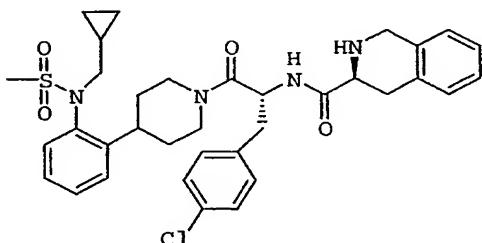
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(0.54 g). MS (ESI, pos. ion) *m/z*: 729 (M+1); MS (ESI, neg. ion) *m/z*: 727 (M-1). Calc'd for C₃₆H₄₂Cl₂N₄O₆S: 728.22.

Step (c) ((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-[(1R)-1-[(3,4-dichlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}piperidyl)-2-oxoethyl]-carboxamide.

To a 150 mL round-bottomed flask equipped with stirring was added *tert*-butyl (3*S*)-3-{N-[(1*R*)-1-[(3,4-dichlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}piperidyl)-2-oxoethyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step b) (0.54 g, 0.74 mmol) followed by a saturated soln of HCl in EtOAc (50 mL). The reaction mixture was stirred at RT for 1 h and concentrated *in vacuo* to a white solid. Recrystallization from MeOH:Et₂O (1:20) provided the title compound (HCl salt) as a white solid (0.3 g). MP 181°C (decomposed). MS (ESI, pos. ion) *m/z*: 629 (M+1); MS (ESI, neg. ion) *m/z*: 627 (M-1). Calc'd for C₃₁H₃₄Cl₂N₄O₄S: 628.17. Anal. Calcd for C₃₁H₃₄Cl₂N₄O₄S·HCl·H₂O: C, 51.71; H, 5.74; N, 7.78; Cl, 14.77. Found: C, 51.66; H, 5.39; N, 7.49; Cl, 15.07.

Example 11



25

N-[(1*R*)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]-

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phenyl)piperidyl)-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl)carboxamide

Step (a) tert-Butyl 4-{2-[(cyclopropylmethyl)

(methylsulfonyl)amino]phenyl}piperidine-carboxylate.

To a 100 mL round-bottomed flask was added *tert*-butyl 4-{2-[(methylsulfonyl)amino]phenyl}piperidine-carboxylate

(Example 1 Step d) (1.9 grams, 5.4 mmol) and DMF (Aldrich) (30 mL). The solution was magnetically stirred vigorously

at 25°C under N₂ atmosphere and treated in portions with NaH as a 60% dispersion in mineral oil (Aldrich) (150 mg, 6.4 mmol). After gas evolution ceased,

(bromomethyl)cyclopropane (Aldrich) (675 μL, 940 mg, 7.0 mmol) was introduced via syringe. The reaction mixture was

stirred at 25°C for 15 h. The reaction was quenched by careful addition of satd NH₄Cl (150 mL) and extracted with EtOAc (400 mL). The organic layer was washed with H₂O (150 mL), satd NaCl (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford the title compound as a

yellow foam (2.2 g). MS (ESI, pos. ion) m/z: 409 (M+1); (ESI, neg. ion) m/z: 407 (M-1). Calc'd for C₂₁H₃₂N₂O₄S: 408.56.

Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-

[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl piperidyl)-2-oxoethyl](tert-butoxy)carboxamide.

To a 100 mL round-bottomed flask was added *tert*-butyl 4-{2-[(cyclopropylmethyl)(methylsulfonyl) amino]-

phenyl}piperidine-carboxylate (Step a) (2.2 g, 5.4 mmol) and CH₂Cl₂ (20 mL). The solution was magnetically stirred and

treated with TFA (Aldrich) (20 mL). After 20 min stirring, the mixture was concentrated *in vacuo*. The resulting yellow film was partitioned between CH₂Cl₂ (150 mL) and satd NaHCO₃ (50 mL). The organic layer was washed with satd NaCl (50

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mL), dried over Na₂SO₄, filtered and concentrated to give a colorless oil (1.7 g).

To a separate 100 mL round-bottomed flask was added Boc-p-
5 Cl-D-PheOH (PepTech Corporation) (2.14 g, 7.17 mmol), DMF
(10 mL) and CH₂Cl₂ (10 mL). The solution was magnetically
stirred at 25°C and treated with DIEA (Aldrich) (3.13 mL,
18.2 mmol), followed by O-(7-azabenzotriazol-1-yl)-1,1,3,3-
tetramethyluronium hexafluorophosphate (PerSeptive
10 Biosystems) (2.72 g, 7.17 mmol). The resulting yellow
solution was stirred for 10 min then treated with a solution
of the colorless oil prepared in the previous paragraph (1.7
g, 5.5 mmol) in CH₂Cl₂ (20 mL). The reaction mixture was
stirred at 25°C for 15 h, diluted with CH₂Cl₂ (300 mL) and
15 washed with water (75 mL), 1 M H₃PO₄ (75 mL), satd NaHCO₃ (75
mL), and satd NaCl (50 mL). The organic layer was dried
over Na₂SO₄, filtered and concentrated *in vacuo* to afford a
yellow oil. The oil was purified by silica gel
chromatography (3:10 EtOAc:hexane) to give the title
20 compound as a white foam (1.99 g). MS (ESI, pos. ion) *m/z*:
590 (M+1); (ESI, neg. ion) *m/z*: 588 (M-1). Calc'd for
C₃₀H₄₀ClN₃O₅S: 590.17.

Step (c) **tert-Butyl 3-{N-[(1R)-1-[(4-chlorophenyl)methyl]-
2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}piperidyl)-2-oxoethyl]carbamoyl}(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.**

To a 10 mL round-bottomed flask was added N-[(1R)-1-[(4-
30 chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]-(*tert*-butoxy)carboxamide (Step b) (450 mg, 0.76 mmol) and CH₂Cl₂ (3 mL). The solution was magnetically stirred and treated with TFA (Aldrich) (3 mL). After stirring 25 min, the

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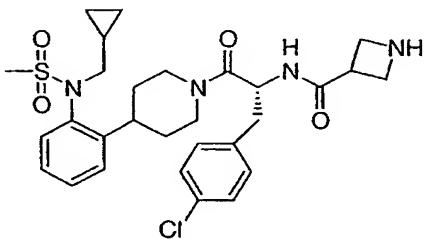
mixture was concentrated *in vacuo* to a yellow film. The film was dissolved in CH₂Cl₂ (50 mL), washed with satd NaHCO₃ (2 x 25 mL), and satd NaCl (25 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a white foam (430 mg). The foam was dissolved in THF (20 mL), added to a 100 mL round-bottomed flask and magnetically stirred. The solution was treated with EDC (Aldrich) (259 mg, 1.35 mmol), followed by HOBT (Aldrich) (267 mg, 1.98 mmol) and Boc-L-TicOH (PepTech Corporation) (305 mg, 1.08 mmol). The reaction mixture was stirred for 18 h at 25°C, and concentrated *in vacuo* to a yellow residue. The residue was partitioned between EtOAc (100 mL) and 1 M H₃PO₄ (75 mL). The aqueous layer was extracted with EtOAc (2 x 25 mL) and the organic layers were combined, washed with 10% Na₂CO₃ (75 mL), satd NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford a yellow oil. Purification by silica gel chromatography (10:25:65 MeOH:EtOAc:hexane) provided the title compound as a white foam (480 mg). MS (ESI, pos. ion) *m/z*: 749 (M+1); (ESI, neg. ion) *m/z*: 747 (M-1). Calc'd for C₄₀H₄₉ClN₄O₆S: 749.36.

Step (d) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide.
To a 250 mL round-bottomed flask equipped with stirring was added *tert*-butyl 3-(N-[(1R)-1-[(4-chlorophenyl)-methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)-amino]phenyl}piperidyl)-2-oxoethyl]carbamoyl) (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step c) (1.9 g, 2.5 mmol) followed by a saturated soln of HCl in EtOAc (150 mL). The mixture was stirred at RT for 1 h then concentrated *in vacuo* to 75 mL, providing a white precipitate. The precipitate was collected by filtration and dried *in vacuo*.

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to provide the HCl salt as a white solid (0.93 g). MS (ESI, pos. ion) m/z : 649 (M+1). Calc'd for $C_{35}H_{41}ClN_4O_4S$: 648.25. Anal. Calcd for $C_{35}H_{41}ClN_4O_4S \cdot 1.1HCl \cdot 1H_2O$: C, 59.28; H, 6.30; N, 7.90; Cl, 10.50. Found: C, 58.95; H, 6.3; N, 7.86; Cl, 10.29. MP 190-200°C.

Example 12



10

N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]azetidin-3-ylcarboxamide

15 Step (a) *tert*-Butyl 3-{N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-piperidyl)-2-

oxoethyl]carbamoyl}azetidine-carboxylate.
The title compound was prepared according to the procedure described in Example 11 (Step c) using N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl](*tert*-butoxy)carboxamide (Example 11 Step b) (450 mg, 0.76 mmol) and 50% TFA in CH_2Cl_2 (6 mL) followed by EDC (Aldrich) (259 mg, 1.35 mmol), HOBT (Aldrich) (270 mg, 2.0 mmol) and N-Boc-azetidine-4-carboxylic acid (PepTech Corporation) (220 mg, 1.1 mmol) in THF (20 mL). Purification by silica gel chromatography (10:25:65 MeOH:EtOAc:hexane) provided the title compound as a white foam (365 mg). MS (ESI, pos. ion)

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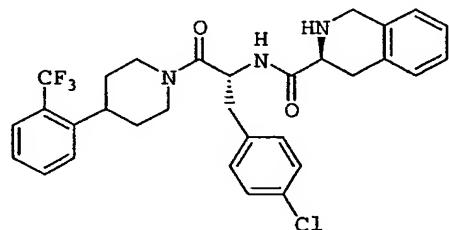
m/z: 673 (*M+1*); (*ESI*, neg. ion) *m/z:* 671 (*M-1*). *Calc'd for*
 $C_{34}H_{45}ClN_4O_6S$: 673.26.

Step (b) N-[(1*R*)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-
 5 [(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}
 piperidyl)-2-oxoethyl]azetidin-3-ylcarboxamide.

The title compound was prepared according to the procedure
 described in Example 3 (Step b) using *tert*-butyl 3-[(1*R*)-
 10 1-[(4-chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-
 (methylsulfonyl)amino]phenyl} piperidyl)-2-
 oxoethyl]carbamoyl]azetidine-carboxylate (Step a) (565 mg,
 0.84 mmol) and 50% TFA in CH_2Cl_2 (6 mL). Purification by
 reverse phase preparative HPLC [YMC-Pack ODS-AM 250 x 20 mm
 5 μ m column, 40% to 75% CH_3CN (0.1% TFA) in H_2O (0.1% TFA)
 15 over 10 min] provided the title compound (TFA salt) as an
 amorphous white solid (420 mg). MS (*ESI*, pos. ion) *m/z:* 573
 (*M+1*). *Calcd for* $C_{29}H_{37}ClN_4O_4S \cdot 1.7C_2HF_3O_2$: C, 50.74; H, 5.09; N, 7.30, S, 4.18.
 Found: C, 50.47; H, 5.03; N, 7.36; S, 4.28.

20

Example 13



25 N-((1*R*)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-{4-[2-
 (trifluoromethyl)phenyl]piperidyl}ethyl)((3*S*)(3-1,2,3,4-
 tetrahydroisoquinolyl))carboxamide

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Step (a) tert-Butyl 4-[2-(trifluoromethyl)phenyl]-1,2,5,6-tetrahydropyridinecarboxylate.

The title compound was prepared according to the procedure described in Preparation A using 2-

5 (trifluoromethyl)phenylboronic acid (Aldrich) (1.89 g, 10 mmol), *tert*-butyl 4-[(trifluoromethyl)sulfonyloxy]-1,2,5,6-tetrahydropyridinecarboxylate [prepared by the method of Wustrow, D. J. and Wise, L. D., *Synthesis*, 1991, 993-995, from *tert*-butyl-4-oxopiperidine-1-carboxylate (Aldrich), LDA 10 (Aldrich) and *N*-phenyltrifluoromethanesulfonimide (Aldrich)] (3.64 g, 11 mmol), tetrakis(triphenylphosphine)palladium (0) (Strem Chemicals) (0.578 g, 0.5 mmol), LiCl (Aldrich) (1.27g, 30 mmol), and Na₂CO₃ (Aldrich) (2.46 g, 30 mmol) in water (15 mL) and DME 15 (20 mL). Purification by silica gel chromatography (5:1 hexane:EtOAc) provided the title compound as a white foam (2.01 g). MS (ESI, pos. ion) *m/z*: 328 (M+1); MS (ESI, neg. ion) *m/z*: 326 (M-1). Calc'd for C₁₇H₂₀F₃NO₂: 327.34.

20 **Step (b) *tert*-Butyl 4-[2-(trifluoromethyl)phenyl]piperidinecarboxylate.**

The title compound was prepared according to the procedure described in Preparation B from *tert*-butyl 4-[2-

25 (trifluoromethyl)phenyl]-1,2,5,6-tetrahydro-pyridinecarboxylate (Step a) (1.96 g, 6.0 mmol) and 10% Pd/C (Aldrich) (0.5 g) in EtOH (30 mL) under 50 psi H₂. The title compound was obtained as white foam (1.87). MS (ESI, pos. ion) *m/z*: 330 (M+1); MS (ESI, neg. ion) *m/z*: 328 (M-1). Calc'd for C₁₇H₂₂F₃NO₂: 329.36.

30

Step (c) 4-[2-(Trifluoromethyl)phenyl]piperidine hydrochloride.

The title compound was prepared according to the procedure described in Example 1 (Step e) from *tert*-butyl 4-[2-

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(trifluoromethyl)phenyl]piperidine carboxylate (Step b) (1.64 g, 5 mmol) and satd HCl in EtOAc (50 mL). The title compound was obtained as a white solid (1.32 g). MS (ESI, pos. ion) m/z : 230 (M+1); MS (ESI, neg. ion) m/z : 228 (M-1). Calc'd for $C_{12}H_{15}ClF_3N$: 265.70.

Step (d) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-{4-[2-(trifluoromethyl)phenyl]-piperidyl}ethyl)(tert-butoxy)carboxamide.

10 The title compound was prepared according to the procedure described in Example 1 (Step f) from 4-[2-(trifluoromethyl)phenyl]piperidine hydrochloride (Step c) (0.792 g, 3.0 mmol), DIEA (0.54 mL, 3.0 mmol), Boc-p-Cl-D-PheOH (PepTech Corporation) (1.36 g, 4.5 mmol), HOAT (Aldrich) (0.615 g, 4.5 mmol) and EDC (Aldrich) (0.864 g, 4.5 mmol) in DMF (5 mL). Purification by silica gel chromatography (5:2 hexane:EtOAc) provided the title compound as a white foam (1.06 g). MS (ESI, pos. ion) m/z : 511 (M+1); MS (ESI, neg. ion) m/z : 509 (M-1). Calc'd for $C_{26}H_{30}ClF_3N_2O_3$: 510.98.

Step (e) (2R)-2-Amino-3-(4-chlorophenyl)-1-{4-[2-(trifluoromethyl)phenyl]-piperidyl}propan-1-one hydrochloride.

25 The title compound was prepared according to the procedure described in Example 1 (Step e) from N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(trifluoromethyl)phenyl]-piperidyl}ethyl)(tert-butoxy)-carboxamide (Step d) (1.02 g, 2.0 mmol) and satd HCl in EtOAc (50 mL). The title compound 30 was obtained as white solid (0.89 g). MS (ESI, pos. ion) m/z : 411 (M+1); MS (ESI, neg. ion) m/z : 409 (M-1). Calc'd for $C_{21}H_{22}ClF_3N_2O$: 410.14.

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Step (f) tert-Butyl 3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(trifluoromethyl)-phenyl]piperidyl}-ethyl)carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

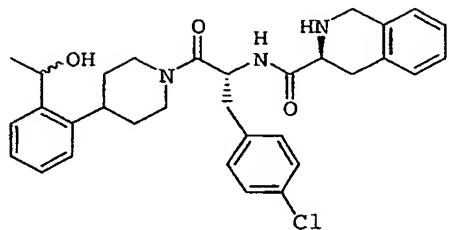
5 The title compound was prepared according to the procedure described in Example 1 (Step f) from (2R)-2-amino-3-(4-chlorophenyl)-1-{4-[2-(trifluoromethyl)-phenyl]piperidyl}propan-1-one hydrochloride (Step e) (890 mg, 2.0 mmol), DIEA (0.40 mL, 2.0 mmol), Boc-L-TicOH (Bachem 10 Company) (544 mg, 2.8 mmol), HOAT (Aldrich) (382 mg, 2.8 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (5:2 hexane:EtOAc) provided the title compound as a white foam (702 mg). MS (ESI, pos. ion) m/z : 670 (M+1); MS (ESI, neg. ion) m/z : 668 (M-1). Calc'd for $C_{36}H_{39}ClF_3N_3O_4$: 669.26.

Step (g) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-{4-[2-(trifluoromethyl)phenyl]-piperidyl}ethyl)((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide trifluoroacetate.

20 The title compound was prepared according to the procedure described in Example 3 (Step b) from *tert*-butyl 3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(trifluoromethyl)-phenyl]piperidyl}ethyl)-carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step f) (335 mg, 0.5 mmol) and 50% TFA in CH_2Cl_2 (20 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) over 30 min, then 100% CH_3CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white solid (202 mg). MS (ESI, pos. ion) m/z : 570 (M+1); (ESI, neg. ion) m/z : 568 (M-1). Calc'd for $C_{31}H_{31}ClF_3N_3O_2$: 569.21.

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Example 14



5 **N-((1R)-1-[(4-Chlorophenyl)methyl]-2-{4-[2-(hydroxyethyl)phenyl]piperidyl}-2-oxoethyl)-((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide**

10 **Step (a) tert-Butyl 4-(2-acetylphenyl)-1,2,5,6-tetrahydropyridinecarboxylate.**

The title compound was prepared according to the procedure described in Preparation A using 2-acetylphenylboronic acid (Aldrich) (1.63 g, 10 mmol), *tert*-butyl 4-[(trifluoromethyl)sulfonyloxy]-1,2,5,6-tetrahydropyridinecarboxylate [prepared by the method of Wustrow, D. J. and Wise, L. D. *Synthesis*, 1991, 993-995, from *tert*-butyl-4-oxopiperidine-1-carboxylate (Aldrich), LDA (Aldrich) and *N*-phenyltrifluoromethane-sulfonimide (Aldrich)] (3.64 g, 11 mmol), 20 tetrakis(triphenylphosphine)palladium (0) (Strem Chemicals) (0.578 g, 0.5 mmol), LiCl (Aldrich) (1.27g, 30 mmol), and Na₂CO₃ (Aldrich) (2.46 g, 30 mmol) in water (15 mL) and DME (20 mL). Purification by silica gel chromatography (5:1 hexane:EtOAc) provided the title compound as a white foam (1.77 g). MS (ESI, pos. ion) *m/z*: 302 (M+1); MS (ESI, neg. ion) *m/z*: 300 (M-1). Calc'd for C₁₈H₂₃NO₃: 301.38.

25 **Step (b) tert-Butyl 4-[2-(hydroxyethyl)phenyl]piperidinecarboxylate.**

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The title compound was prepared according to the procedure described in Preparation B using *tert*-butyl 4-(2-acetylphenyl)-1,2,5,6-tetrahydropyridine carboxylate (Step a) (1.51 g, 5.0 mmol) and 10% Pd/C (Aldrich) (0.5 g) in MeOH (30 mL) under 50 psi H₂ for 48 h. The title compound was obtained as a white foam (1.49 g). MS (ESI, pos. ion) m/z: 306 (M+1); MS (ESI, neg. ion) m/z: 304 (M-1). Calc'd for C₁₈H₂₇NO₃: 305.41.

10 **Step (c) 1-(2-(4-Piperidyl)phenyl)ethan-1-ol hydrochloride.**

The title compound was prepared according to the procedure described in Example 1 (Step e) using *tert*-butyl 4-[2-(hydroxyethyl)phenyl]piperidinecarboxylate (Step b) (1.22 g, 4.0 mmol) and satd anhydrous HCl in EtOAc (50 mL). The title compound was obtained as a white solid (0.96 g). MS (ESI, pos. ion) m/z: 206 (M+1); MS (ESI, neg. ion) m/z: 204 (M-1). Calc'd for C₁₃H₁₉NO: 205.15.

20 **Step (d) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-[2-**

(hydroxyethyl)phenyl]piperidyl]-2-oxoethyl)(*tert*-butoxy)carboxamide.

The title compound was prepared according to the procedure described in Example 1 (Step f) using 1-(2-(4-piperidyl)phenyl)ethan-1-ol hydrochloride (Step c) (0.72 g, 3.0 mmol), DIEA (0.54 mL, 3.0 mmol), Boc-p-Cl-D-PheOH (PepTech Corporation) (1.36 g, 4.5 mmol), HOAT (Aldrich) (0.615 g, 4.5 mmol) and EDC (Aldrich) (0.864 g, 4.5 mmol) in DMF (5 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (1.09 g). MS (ESI, pos. ion) m/z: 487 (M+1); MS (ESI, neg. ion) m/z: 485 (M-1). Calc'd for C₂₇H₃₅ClN₂O₄: 486.23.

30 **Step (e) (2R)-2-Amino-3-(4-chlorophenyl)-1-[2-(hydroxyethyl)phenyl]piperidyl]-propan-1-one hydrochloride.**

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The title compound was prepared according to the procedure described in Example 1 (Step e) using N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(hydroxyethyl)phenyl]piperidyl}-2-oxoethyl) (tert-butoxy)carboxamide (Step d) (0.976 g, 2.0 mmol) and satd anhydrous HCl in EtOAc (30 mL). The title compound was obtained as a white solid (0.846 g). MS (ESI, pos. ion) m/z: 387 (M+1); MS (ESI, neg. ion) m/z: 385 (M-1). Calc'd for C₂₂H₂₇ClN₂O₂: 386.18.

10

Step (f) *tert-Butyl 3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(hydroxyethyl)phenyl]piperidyl}-2-oxoethyl)carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.*

15 The title compound was prepared according to the procedure described in Example 1 (Step f) using (2R)-2-amino-3-(4-chlorophenyl)-1-{4-[2-(hydroxyethyl)phenyl]piperidyl}-propan-1-one hydrochloride (Step e) (846 mg, 2.0 mmol), DIEA (0.40 mL, 2.0 mmol), Boc-L-TicOH (Bachem Company) (544 mg, 2.8 mmol), HOAT (Aldrich) (382 mg, 2.8 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (10 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (739 mg). MS (ESI, pos. ion) m/z: 646 (M+1); MS (ESI, neg. ion) m/z: 644 (M-1). Calc'd for C₃₇H₄₄ClN₃O₅: 645.30.

20
25
Step (g) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-{4-[2-(hydroxyethyl)phenyl]piperidyl}-2-oxoethyl)((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide.

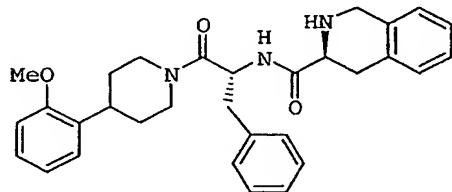
30 The title compound was prepared according to the procedure described in Example 3 (Step b) using *tert*-butyl 3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(hydroxyethyl)phenyl]piperidyl}-2-oxoethyl)carbamoyl]-(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step f) (323 mg, 0.5

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mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 µm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the 5 title compound (TFA salt) as a white solid (145 mg). MS (ESI, pos. ion) *m/z*: 546 (M+1); (ESI, neg. ion) *m/z*: 544 (M-1). Calc'd for C₃₂H₃₆ClN₃O₃: 545.24.

Example 15

10



((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-((1R)-2-[4-(2-methoxyphenyl)piperidyl]-2-oxo-1-benzylethyl)carboxamide

15

Step (a) N-((1R)-2-[4-(2-Methoxyphenyl)piperidyl]-2-oxo-1-benzylethyl)(tert-butoxy)carboxamide.

The title compound was prepared according to the procedure described in Example 1 (Step f) using 4-(2-methoxyphenyl)piperidine (Maybridge) (2.68 g, 0.014 mol), Boc-D-PheOH (Advanced ChemTech) (3.71 g, 0.014 mol), HOAT (Aldrich) (1.9 g, 0.014 mol) and EDC (Advanced ChemTech) (4.02 g, 0.021 mol). Purification by silica gel chromatography (1:1 EtOAc:hexane) provided the title 20 compound as a colorless oil (5.0 g). MS (ESI, pos. ion) *m/z*: 439 (M+1). Calc'd for C₂₆H₃₄N₂O₄: 438.56.

Step (b) tert-Butyl (3S)-3-(N-((1R)-2-[4-(2-methoxyphenyl)piperidyl]-2-oxo-1-benzylethyl)carbamoyl)-30 1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

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The title compound was prepared according to the procedure described in Example 10 (Step b) using N-((1R)-2-[4-(2-methoxyphenyl)piperidyl]-2-oxo-1-benzylethyl)(tert-butoxy)carboxamide (Step a) (5.0 g, 11 mmol) and satd anhydrous HCl in EtOAc (70 mL) which provided a white solid (4.11 g, 100%). A portion of the white solid (1.2 g, 3.2 mmol) was treated with Boc-L-TicOH (Advance ChemTech) (0.887 g, 3.2 mmol), HOAT (Aldrich) (0.435 g, 3.2 mmol), TEA (Aldrich) (0.67 mL, 4.8 mmol) and EDC (Advanced ChemTech) (0.92 g, 4.8 mmol). Purification by silica gel chromatography (1:1 EtOAc:hexane then 100% EtOAc) provided the title compound as a white foam (1.4 g). MS (ESI, pos. ion) m/z : 598 (M+1); (ESI, neg. ion) m/z : 596 (M-1). Calc'd for $C_{36}H_{43}N_3O_5$: 597.32.

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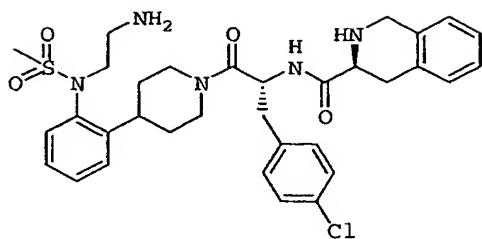
Step (c) ((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-((1R)-2-[4-(2-methoxyphenyl)-piperidyl]-2-oxo-1-benzylethyl)carboxamide.

The title compound was prepared according to the procedure described in Example 3 (Step b) from tert-butyl (3S)-3-(N-((1R)-2-[4-(2-methoxyphenyl)piperidyl]-2-oxo-1-benzylethyl)carbamoyl)-1,2,3,4-tetrahydro-isoquinoline-2-carboxylate (Step b) (1.4 g, 2.34 mmol) and 50% TFA in CH_2Cl_2 (80 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) over 30 min, then 100% CH_3CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (0.5 g). MS (ESI, pos. ion) m/z : 498 (M+1). Calc'd for $C_{31}H_{35}N_3O_3$: 497.27.

30

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Example 16



5

N-[(1R)-2-(4-{2-[(2-aminoethyl)(methylsulfonyl)amino]phenyl}piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-carboxamide

10 **Step (a) *tert*-Butyl 4-(2-[(2-(1,3-dioxoisindolin-2-yl)ethyl](methylsulfonyl)-amino]phenyl)piperidinecarboxylate.**

To a 250 mL round-bottomed flask equipped with stirring was added *tert*-butyl 4-(2-[(methylsulfonyl)-amino]phenyl)piperidine-carboxylate (Example 1 Step d) (2.12 g, 6.0 mmol), DMF (100 mL), *N*-(2-bromomethyl)-phthalimide (Aldrich) (4.57 g, 18 mmol) and K₂CO₃ (Aldrich) (7.45 g, 54 mmol). The mixture was stirred at 75°C for 24 h, filtered and concentrated *in vacuo* to afford a yellow oil. The oil 15 was dissolved in a 1:1 mixture of EtOAc in THF (100 mL), washed with 0.1 M HCl (100 mL), satd NaCl (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (1:1 hexane:EtOAc) to provide the title compound as a white foam 20 (1.98 g). MS (ESI, pos. ion) *m/z*: 528 (M+1); MS (ESI, neg. ion) *m/z*: 526 (M-1). Calc'd for C₂₇H₃₃N₃O₆S: 527.21.

25

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Step (b) 2-{2-[(Methylsulfonyl)(2-(4-piperidyl)phenyl)amino]ethyl}isoindoline-1,3-dione hydrochloride.

To a 150 mL round-bottomed flask equipped with stirring was
5 added *tert*-butyl 4-(2-[(2-(1,3-dioxo-isoindolin-2-
yl)ethyl)(methylsulfonyl)-amino]-phenyl)-
piperidinecarboxylate (Step a) (1.58 g, 3 mmol) and EtOAc (5
mL). The mixture was treated with a satd solution of
anhydrous HCl in EtOAc (70 mL) at 0°C. The reaction mixture
10 was warmed to RT and stirred for 3 h. The solvent was
removed *in vacuo* to provide the title compound as a white
foam (1.38 g). MS (ESI, pos. ion) *m/z*: 428 (M+1); MS (ESI,
neg. ion) *m/z*: 426 (M-1). Calc'd for C₂₂H₂₅N₃O₄S: 427.16.

15 **Step (c) N-[(1R)-2-[4-(2-[(1,3-Dioxoisoindolin-2-
yl)ethyl](methylsulfonyl)-amino)phenyl]-piperidyl]-1-[(4-
chlorophenyl)methyl]-2-oxoethyl](*tert*-butoxy)carboxamide.**

The title compound was prepared according to the procedure
described in Example 1, (Step f) from 2-{2-
20 [(methylsulfonyl)(2-(4-piperidyl)phenyl)amino]ethyl}
isoindoline-1,3-dione hydrochloride (Step b) (1.28 g, 2.8
mmol), DIEA (0.54 mL, 3.0 mmol), Boc-p-Cl-D-PheOH (PepTech
Corporation) (1.36 g, 4.5 mmol), HOAT (Aldrich) (0.615 g,
4.5 mmol) and EDC (Aldrich) (0.864 g, 4.5 mmol) in DMF (15
mL). Purification by silica gel chromatography (1:1
25 hexane:EtOAc) provided the title compound as a white foam
(1.83 g%). MS (ESI, pos. ion) *m/z*: 709 (M+1); MS (ESI,
neg. ion) *m/z*: 707 (M-1). Calc'd for C₃₆H₄₁ClN₄O₇S : 708.24.

30 **Step (d) 2-{2-[(2-{1-[(2R)-2-Amino-3-(4-chlorophenyl)propanoyl}(4-piperidyl)}phenyl)-
(methylsulfonyl)amino]ethyl}isoindoline-1,3-dione
hydrochloride.**

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The title compound was prepared according to the procedure described in (Step b) from N-((1R)-2-[4-(2-[(2-(1,3-dioxoisoindolin-2-yl)ethyl](methylsulfonyl)-amino]phenyl)-piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)(tert-
5 butoxy)carboxamide (Step c) (1.77 g, 2.5 mmol) and satd anhydrous HCl in EtOAc (50 mL). The title compound was obtained as a white solid (1.61 g). MS (ESI, pos. ion) m/z: 609 (M+1); MS (ESI, neg. ion) m/z: 607 (M-1). Calc'd for C₃₁H₃₄Cl₂N₄O₅S: 645.60.

10

Step (e) **tert-Butyl 3-(N-((1R)-2-[4-(2-[(2-(1,3-dioxoisoindolin-2-yl)ethyl](methylsulfonyl)-amino]phenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.**

15

The title compound was prepared according to the procedure described in Example 1 (Step f) using 2-{2-[(2-{1-[(2R)-2-amino-3-(4-chlorophenyl)propanoyl}(4-piperidyl)phenyl)-(methylsulfonyl)amino]ethyl}isoindoline-1,3-dione hydrochloride (Step d) (643 mg, 1.0 mmol), DIEA (0.20 mL, 1.0 mmol), Boc-L-TicOH (Bachem Company) (394 mg, 1.42 mmol), HOAT (Aldrich) (232 mg, 1.70 mmol) and EDC (Aldrich) (544 mg, 2.84 mmol) in DMF (5 mL). Purification by silica gel chromatography (3:2 hexane:EtOAc) provided the title compound as a white foam (628 mg). MS (ESI, pos. ion) m/z: 868 (M+1); MS (ESI, neg. ion) m/z: 866 (M-1). Calc'd for C₄₆H₅₀ClN₅O₈S: 867.31.

20

Step (f) **tert-Butyl 3-(N-((1R)-2-(4-{2-[(2-aminoethyl)(methylsulfonyl)amino]phenyl}-piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.**

To a 50 mL round-bottomed flask equipped with stirring was added a solution of **tert-butyl 3-(N-((1R)-2-[4-(2-[(2-(1,3-**

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dioxoisoindolin-2-yl)ethyl] (methylsulfonyl)-
amino}phenyl)piperidyl]-1-[{4-chlorophenyl)methyl]-2-
oxoethyl}carbamoyl) (3S)-1,2,3,4-tetrahydroisoquinoline-2-
carboxylate (Step e) (433.5 mg, 0.5 mmol) in 3:1 EtOH:1,2-
5 dichloroethane (15 mL) followed by hydrazine (Aldrich) (49
mg, 1.5 mmol). The reaction mixture was stirred at 60°C for
12 h. The organic solvents were removed *in vacuo* to provide
a white solid which was dissolved in EtOAc (20 mL) and
washed with satd NaHCO₃ (20 mL) and satd NaCl (20 mL). The
10 organic layer was dried over Na₂SO₄, filtered and
concentrated *in vacuo*. Purification by silica gel
chromatography (100% EtOAc) provided the title compound as a
white foam (349 mg). MS (ESI, pos. ion) *m/z*: 738 (M+1); MS
(ESI, neg. ion) *m/z*: 736 (M-1). Calc'd for C₃₈H₄₈ClN₅O₆S:
15 737.30.

Step (g) N-[(1R)-2-(4-{2-[(2-Aminoethyl)(methylsulfonyl)
amino}phenyl)piperidyl]-1-[{4-chlorophenyl)methyl]-2-
oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-
20 carboxamide.

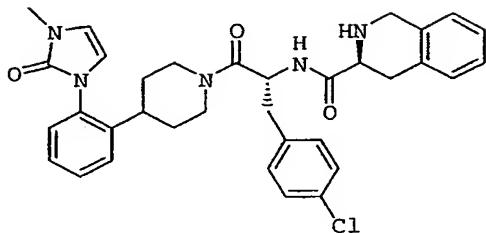
The title compound was prepared according to the procedure
described in Example 3 (Step b) from *tert*-butyl 3-(N-[(1R)-
2-(4-{2-[(2-aminoethyl)-
(methylsulfonyl)amino}phenyl)piperidyl]-1-[{4-
25 chlorophenyl)methyl]-2-oxoethyl]carbamoyl) (3S)-1,2,3,4-
tetrahydroisoquinoline-2-carboxylate (Step f) (294.8 mg, 0.4
mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by
reverse phase preparative HPLC [Phenomenex; 5 μm 250 x 21.2
mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30
30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the
title compound (TFA salt) as a white solid (224 mg). MS
(ESI, pos. ion) *m/z*: 638 (M+1); (ESI, neg. ion) *m/z*: 636
(M-1). Calc'd for C₃₃H₄₀ClN₅O₄S: 637.25. Anal. Calcd for

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$C_{33}H_{40}ClN_5O_4S \cdot 2.5C_2HF_3O_2$: C, 49.43; H, 4.64; N, 7.41. Found: C, 49.39; H, 4.78; N, 7.58.

Example 17

5



10 ((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)phenyl]piperidyl}-2-oxoethyl)carboxamide

Step (a) tert-Butyl 4-(2-{[(2,2-dimethoxyethyl)methylamino]carbonylamino}-phenyl)piperidinecarboxylate.

The title compound was prepared according to the procedures described by WO01/44230, Wong, O. et al. (*Heterocycles* 1987, 26, 3153-8) and Ciufolini and Xi, J. Org. Chem., 62, 2320-21 (1997). To a 50 mL round-bottomed flask equipped with stirring was added Preparation B (0.85 g, 3.08 mmol), *N,N'*-disuccinimidyl carbonate (Aldrich) (1.57 g, 6.16 mmol) and DMF (10 mL). The reaction mixture was stirred for 12 h at RT. A solution of methylaminoacetylaldehyde dimethylacetal (1.0 mL, 7.78 mmol) (Aldrich) in 5:2 DMF:CH₂Cl₂ (7 mL) was added via syringe and stirring was continued for an additional 12 h. The reaction mixture was diluted with EtOAc (50 mL) and the organic phase washed with satd NaHCO₃ (40 mL), satd NaCl (40 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by silica gel chromatography (1:1 EtOAc:hexane then 100% EtOAc) provided

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the title compound as a yellow oil (1.04 g). MS (ESI, pos. ion) *m/z*: 422 (M+1). Calc'd for C₂₂H₃₅N₃O₅ : 421.26.

Step (b) N-((1*R*)-1-[(4-Chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)-phenyl]piperidyl}-2-oxoethyl)(tert-butoxy)carboxamide.

To a 150 mL round-bottomed flask equipped with stirring was added tert-butyl 4-(2-[(2,2-dimethoxyethyl)methylamino]carbonylamino)phenyl-piperidinecarboxylate (Step a) (1.4 g, 3.3 mmol) and a 50% aqueous TFA soln (50 mL). The reaction mixture was stirred at RT for 2 h, then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (10 mL), stirred at 0°C and treated with Boc-p-Cl-D-PheOH (Advanced ChemTech) (0.94 g, 3.15 mmol), HOBT (Novabiochem) (0.425 g, 3.15 mmol), TEA (Aldrich) (0.44 mL, 3.15 mmol) and EDC (Advanced ChemTech) (0.91 g, 4.7 mmol). The reaction was warmed to RT over 2 h and stirred at RT for 12 h. The reaction mixture was diluted with CH₂Cl₂ (60 mL) and the organic phase was washed with satd NaHCO₃ (50 mL), and satd NaCl (50 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification by silica gel chromatography (100% EtOAc) provided the title compound as a pale yellow oil (0.55 g). MS (ESI, pos. ion) *m/z*: 539 (M+1). Calc'd for C₂₉H₃₅ClN₄O₄: 538.23.

25

Step (c) tert-Butyl (3*S*)-3-[N-((1*R*)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)-phenyl]piperidyl}-2-oxoethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

30 The title compound was prepared according to the procedure described in Example 10 (Step b) using N-((1*R*)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)-phenyl]piperidyl}-2-oxoethyl)(tert-butoxy)carboxamide (Step b) (0.237 g, 0.44 mmol) and satd

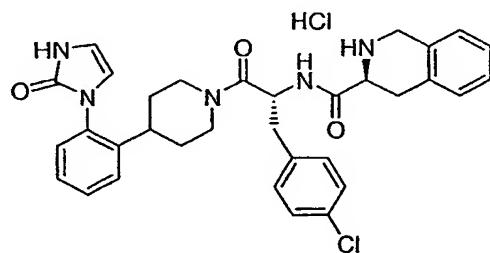
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anhydrous HCl in EtOAc, followed by Boc-L-TicOH (Advanced ChemTech) (0.123 g, 0.44 mmol), HOAT (Aldrich) (0.06 g, 0.44 mmol), TEA (Aldrich) (0.06 mL, 0.44 mmol) and EDC (Advanced ChemTech) (0.126 g, 0.66 mmol) in DMF (10 mL). Purification 5 by silica gel chromatography (EtOAc then 1:9 MeOH:EtOAc) provided the title compound as a pale yellow foam (0.12 g). MS (ESI, pos. ion) m/z : 698 (M+1). Calc'd for $C_{39}H_{44}ClN_5O_5$: 697.30.

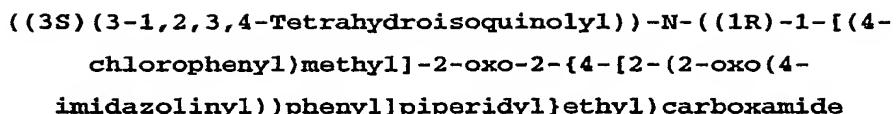
10 **Step (d) ((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)phenyl]piperidyl}-2-oxoethyl)carboxamide.**
 The title compound was prepared according to the procedure described in Example 10 (Step c) from *tert*-butyl (3S)-3-[N-
 15 ((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)phenyl]piperidyl}-2-oxoethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step c) (0.12 g, 0.17 mmol) and satd anhydrous HCl in EtOAc (50 mL). Recrystallization from 1:10 CH₂Cl₂:Et₂O provided the title
 20 compound (HCl salt) as a white solid (0.06 g). MP 178°C (decomposed). MS (ESI, pos. ion) m/z : 598 (M+1). Calc'd for C₃₄H₃₆ClN₅O₃: 597.25. Anal. Calcd for C₃₄H₃₆ClN₅O₃·HCl·1.25H₂O: C, 62.15; H, 6.06; N, 10.66; Cl, 10.79. Found: C, 62.20; H, 6.02; N, 10.68; Cl, 10.65.

25

Example 18



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5 **Step (a) tert-Butyl 4-[(2,2-dimethoxyethyl)amino]-carbonylamino}phenyl)piperidine-carboxylate.**

The title compound was prepared according to the procedure described in Example 17 (Step a) WO01/44230, Wong, O. et al. (*Heterocycles* 1987, 26, 3153-8) and Ciufolini and Xi, J.

10 Org. Chem., 62, 2320-21 (1997) from *tert*-butyl 4-(2-aminophenyl)piperidinecarboxylate (0.85 g, 3.08 mmol), *N,N'*-disuccinimidyl carbonate (Aldrich) (1.57 g, 6.16 mmol) and aminoacetylaldehyde dimethylacetal (Aldrich) (1.0 mL, 9.18 mmol). Purification by silica gel chromatography (1:1 EtOAc:hexane then 100% EtOAc) provided the title compound as a yellow oil (0.742 g). MS (ESI, pos. ion) *m/z*: 408 (M+1). Calc'd for C₂₁H₃₃N₃O₅ : 407.24.

Step (b) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-{4-[2-

20 **(2-oxo(4-imidazolinyl)phenyl)-piperidyl]ethyl)(tert-butoxy)carboxamide.**

The title compound was prepared according to the procedure described in Example 17 (Step b) using *tert*-butyl 4-(2-[(2,2-dimethoxyethyl)amino]carbonylamino}

25 phenyl)piperidine-carboxylate (Step a) (0.742 g, 1.82 mmol) and a 50% aqueous TFA soln (20 mL) followed by Boc-p-Cl-D-PheOH (Advanced ChemTech) (0.545 g, 1.82 mmol), EDC (Advanced ChemTech) (0.523 g, 2.73 mmol), HOBT (Novabiochem) (0.246 g, 1.82 mmol) and TEA (Aldrich) (0.25 mL, 1.82 mmol) 30 in CH₂Cl₂ (10 mL). Purification by silica gel chromatography (100% EtOAc then 1:9 MeOH:EtOAc) provided the title compound as a white solid (0.675 g). MS (ESI, pos. ion) *m/z*: 525 (M+1). Calc'd for C₂₈H₃₃ClN₄O₄: 524.22.

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Step (c) tert-Butyl (3S)-3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl]piperidyl}ethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

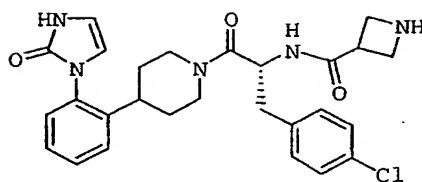
5 The title compound was prepared according to the procedure described in Example 10 (Step b) using N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl]piperidyl}ethyl) (tert-butoxy)carboxamide (Step b) (0.283 g, 0.54 mmol) and satd
10 anhydrous HCl in EtOAc, followed by Boc-L-TicOH (Advanced ChemTech) (0.18 g, 0.65 mmol), EDC (Advanced ChemTech) (0.155 g, 0.81 mmol), HOBT (Novabiochem) (0.073 g, 0.54 mmol) and TEA (Aldrich) (0.075 mL, 0.54 mmol) in CH₂Cl₂ (10 mL). Purification by silica gel chromatography (100% EtOAc
15 then 1:9 MeOH:EtOAc) provided the title compound as a white foam (0.3 g). MS (ESI, pos. ion) *m/z*: 684 (M+1). Calc'd for C₃₈H₄₂ClN₅O₅: 683.29.

Step (d) ((3S)(3-1,2,3,4-Tetrahydroisoquinolyl))-N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl]piperidyl}ethyl)carboxamide.

The title compound was prepared according to the procedure described in Example 10 (Step c) from *tert*-butyl (3S)-3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl]piperidyl}ethyl) carbamoyl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step c) (0.3 g, 0.44 mmol) and satd anhydrous HCl in EtOAc (20 mL). Recrystallization from 1:20 MeOH:Et₂O provided the title compound (HCl salt) as a white solid (0.15 g). MP 191°C
30 (decomposed). MS (ESI, pos. ion) *m/z*: 584 (M+1). Calc'd for C₃₃H₃₄ClN₅O₃: 597.25. Anal. Calcd for C₃₃H₃₄ClN₅O₃·HCl·2.25H₂O: C, 59.95; H, 6.02; N, 10.59; Cl, 10.73. Found: C, 59.93; H, 5.83; N, 10.45; Cl, 10.57.

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Example 19



5 **N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl))phenyl]-piperidyl}ethyl)azetidin-3-ylcarboxamide**

Step (a) **tert-Butyl 3-[N-((1R)-1-[(4-chlorophenyl)-methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl))-phenyl]piperidyl}ethyl)carbamoyl]azetidinecarboxylate.**

The title compound was prepared according to the procedure described in Example 10 (Step b) using N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl))phenyl]-piperidyl}ethyl) (tert-butoxy)carboxamide (Example 18 Step b) (0.227 g, 0.433 mmol) and satd HCl in EtOAc (20 mL), followed by Boc-azetidine-3-carboxylic acid (PepTech Corporation) (0.105 g, 0.52 mmol), EDC (Advanced ChemTech) (0.125 g, 0.65 mmol), HOBT (Novabiochem) (0.058 g, 0.433 mmol) and TEA (Aldrich) (0.058 mL, 0.433 mmol) in CH₂Cl₂ (10 mL). Purification by silica gel chromatography (100% EtOAc then 1:9 MeOH:EtOAc) provided the title compound as a white foam (0.2 g). MS (ESI, pos. ion) *m/z*: 608 (M+1). Calc'd for C₃₂H₃₈ClN₅O₅: 607.26.

Step (b) **N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl))phenyl]-piperidyl}ethyl)azetidin-3-ylcarboxamide.**

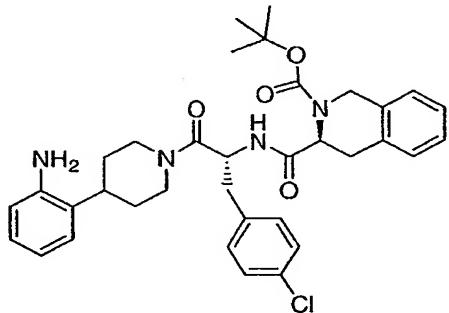
The title compound was prepared according to the procedure described in Example 16 (Step b) using *tert*-butyl 3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-

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imidazolinyl)phenylpiperidyl} ethyl)carbamoyl]azetidinecarboxylate (Step a) (0.2 g, 0.33 mmol) and satd anhydrous HCl in EtOAc (20 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white solid (0.02 g). MS (ESI, pos. ion) *m/z*: 508 (M+1). Calc'd for C₂₇H₃₀ClN₅O₃: 507.20.

10

Example 20



15 **tert-Butyl 3-(N-((1R)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate**

20 **Step (a) tert-Butyl 4-[(2-[(fluoren-9-yl)methoxy]carbonylamino)phenyl]piperidine-carboxylate.**
To a 250 mL round-bottomed flask equipped with stirring was added Preparation B (5.52 g, 20 mmol) followed by 1,2-dichloroethane (100 mL) and DIEA (Aldrich) (4.4 mL, 22 mmol). The reaction mixture was stirred for 5 min at RT, then treated with 9-fluorenylmethylchloroformate (Aldrich) (5.69 g, 22 mmol). After stirring for 8 h at RT, the reaction was quenched by the addition of satd NH₄Cl (60 mL).

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The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The organic fractions were combined, washed with satd NaCl, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (5:1 hexane:EtOAc) provided the title compound as a pale yellow foam (8.96 g). MS (ESI, pos. ion) m/z: 499 (M+1); MS (ESI, neg. ion) m/z: 497 (M-1). Calc'd for C₃₁H₃₄N₂O₄: 498.25.

10 **Step (b) (Fluoren-9-ylmethoxy)-N-(2-(4-piperidyl)phenyl)carboxamide hydrochloride.**

The title compound was prepared according to the procedure described in Example 16 (Step b) from *tert*-butyl 4-{2-[(fluoren-9-ylmethoxy)carbonylamino]phenyl} piperidine-15 carboxylate (Step a) (7.49 g, 15 mmol) and satd anhydrous HCl in EtOAc (50 mL). The title compound was obtained as a white solid (6.51 g). MS (ESI, pos. ion) m/z: 399 (M+1); MS (ESI, neg. ion) m/z: 397 (M-1). Calc'd for C₂₆H₂₇ClN₂O₂: 398.20.

20

Step (c) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-[(fluoren-9-ylmethoxy)carbonylamino]phenyl)piperidyl]-2-oxoethyl](*tert*-butoxy)carboxamide.

The title compound was prepared according to the procedure described in Example 1 (Step f) from (fluoren-9-ylmethoxy)-N-(2-(4-piperidyl)phenyl)-carboxamide hydrochloride (Step b) (6.51 g, 15 mmol), DIEA (2.7 mL, 15 mmol), Boc-p-Cl-D-PheOH (PepTech Corporation) (6.8 g, 22.5 mmol), HOAT (Aldrich) (3.1 g, 22.5 mmol) and EDC (Aldrich) (4.32 g, 22.5 mmol) in DMF (25 mL). Purification by silica gel chromatography (3:1 hexane:EtOAc) provided the title compound as a white foam (6.87 g). MS (ESI, pos. ion) m/z: 680 (M+1); MS (ESI, neg. ion) m/z: 678 (M-1). Calc'd for C₄₀H₄₂ClN₃O₅: 679.28.

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Step (d) N-(2-{1-[(2R)-2-Amino-3-(4-chlorophenyl)propanoyl](4-piperidyl)phenyl}(fluoren-9-ylmethoxy)carboxamide hydrochloride.

5 The title compound was prepared according to the procedure described in Example 16 (Step b) from N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(fluoren-9-ylmethoxy)carbonylamino]-phenyl}piperidyl)-2-oxoethyl](tert-butoxy)carboxamide (Step c) (6.8 g, 10 mmol) and satd
10 anhydrous HCl in EtOAc (50 mL). The title compound was obtained as a white solid (6.1 g). MS (ESI, pos. ion) m/z: 580 (M+1); MS (ESI, neg. ion) m/z: 578 (M-1). Calc'd for C₃₅H₃₅Cl₂N₃O₃: 579.23.

15 **Step (e) tert-Butyl 3-(N-[(1R)-1-[(4-chlorophenyl)-methyl]-2-(4-{2-[(fluoren-9-ylmethoxy)carbonylamino]-phenyl}piperidyl)-2-oxoethyl]carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.**

The title compound was prepared according to the procedure
20 described in Example 1 (Step f) from N-(2-{1-[(2R)-2-amino-3-(4-chlorophenyl)propanoyl](4-piperidyl)phenyl}(fluoren-9-ylmethoxy)carboxamide hydrochloride (Step d) (6.1 g, 9.9 mmol), DIEA (2.0 mL, 10 mmol), Boc-L-TicOH (Bachem Company) (4.16 g, 15 mmol), HOAT (Aldrich) (2.04 g, 15 mmol) and EDC (Aldrich) (2.87 g, 15 mmol) in DMF (25 mL). Purification by
25 silica gel chromatography (3:1 hexane:EtOAc) provided the title compound as a white foam (7.09 g). MS (ESI, pos. ion) m/z: 839 (M+1); MS (ESI, neg. ion) m/z: 837 (M-1). Calc'd for C₅₀H₅₁ClN₄O₆: 838.35.

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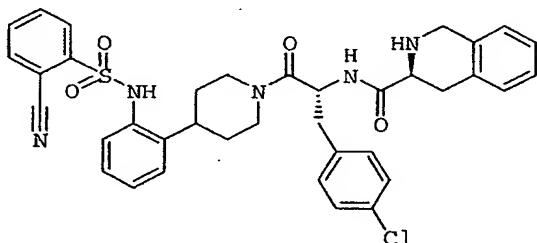
Step (f) tert-Butyl 3-(N-[(1R)-2-[4-(2-aminophenyl)-piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl]-carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

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The title compound was prepared according to the procedure described in Example 8 (Step b) using *tert*-butyl 3-{N-[(1*R*)-1-[(4-chlorophenyl)methyl]-2-[4-[(2-[(fluoren-9-yl)methoxy]carbonylamino)phenyl]piperidyl]-2-oxoethyl]carbamoyl} (3*S*)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step e) (5.88 g, 7.0 mmol), *n*-octanethiol (Aldrich) (1.23 g, 8.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (Aldrich) (63.8 mg, 0.42 mmol) in THF (50 mL). The title compound was obtained as a yellow solid (3.73 g). MS (ESI, pos. ion) *m/z*: 617 (M+1); MS (ESI, neg. ion) *m/z*: 615 (M-1). Calc'd for C₃₅H₄₁ClN₄O₄: 618.28.

Example 21

15



20 N-((1*R*)-1-[(4-Chlorophenyl)methyl]-2-[4-[(2-cyanophenyl)sulfonyl]amino]-phenyl)piperidyl)-2-oxoethyl}((3*S*)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide

Step (a) *tert*-Butyl 3-{N-[(1*R*)-1-[(4-chlorophenyl)methyl]-2-[4-[(2-cyanophenyl)sulfonyl]amino]-phenyl)piperidyl]-2-oxoethyl}carbamoyl} (3*S*)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

To a 50 mL round-bottomed flask equipped with stirring was added *tert*-butyl 3-{N-[(1*R*)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl]carbamoyl} (3*S*)-1,2,3,4-tetrahydroisoquinoline-2-

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carboxylate (Example 20) (154 mg, 0.25 mmol), 1,2-dichloroethane (10 mL) and pyridine (0.03 mL, 0.375 mmol). The reaction mixture was stirred for 5 min at RT, treated with 2-cyanobenzenesulfonyl chloride (Lancaster Synthesis) (50 mg, 0.25 mmol) and stirred at RT for 16 h. The reaction was quenched with satd NH₄Cl (10 mL), the organic layer separated, and the aqueous layer extracted with CH₂Cl₂ (2 x 10 mL). The organic fractions were combined, washed with satd NaCl (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (167 mg). MS (ESI, pos. ion) m/z: 782 (M+1); MS (ESI, neg. ion) m/z: 780 (M-1). Calc'd for C₄₂H₄₄ClN₅O₆S: 781.27.

15

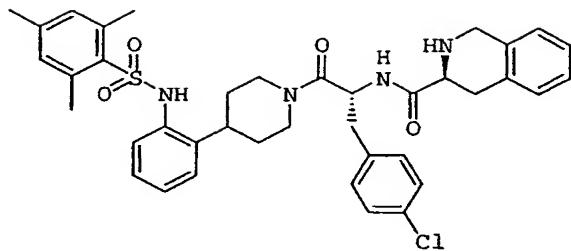
Step (b) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-[4-(2-[(2-cyanophenyl)sulfonyl]amino)phenyl]piperidyl)-2-oxoethyl)((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-carboxamide.

20

The title compound was prepared according to the procedure described in Example 3 (Step b) using tert-butyl 3-((1R)-1-[(4-chlorophenyl)methyl]-2-[4-(2-[(2-cyanophenyl)sulfonyl]amino)phenyl]piperidyl)-2-oxoethyl carbamoyl) (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step a) (167 mg, 0.21 mmol) and 50% TFA in CH₂Cl₂ (10 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (76 mg). MS (ESI, pos. ion) m/z: 682 (M+1); (ESI, neg. ion) m/z: 680 (M-1). Calc'd for C₃₇H₃₆ClN₅O₄S: 681.22.

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Example 22



5 **N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-[4-(2-[(2,4,6-trimethylphenyl)sulfonyl]amino)phenyl]piperidyl)ethyl((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide**

10 **Step (a) tert-Butyl 3-(N-((1R)-1-[(4-chlorophenyl)-methyl]-2-oxo-2-[4-(2-[(2,4,6-trimethylphenyl)-sulfonyl]-amino)phenyl)piperidyl]-ethyl)carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.**

The title compound was prepared according to the procedure described in Example 21 (Step a) by treating *tert*-butyl 3-(N-((1R)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Example 20) (154 mg, 0.25 mmol) with 2-mesitylenesulfonyl chloride (Aldrich) (55 mg, 0.25 mmol) and pyridine (0.03 mL, 0.375 mmol) in 1,2-dichloroethane (10 mL). Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (146 mg). MS (ESI, pos. ion) *m/z*: 799 (M+1); MS (ESI, neg. ion) *m/z*: 797 (M-1). Calc'd for C₄₄H₅₁ClN₄O₆S: 798.32.

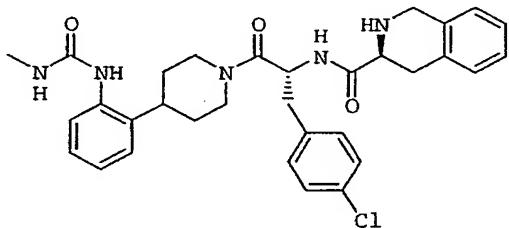
Step (b) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-oxo-2-[4-(2-[(2,4,6-trimethylphenyl)sulfonyl]amino)-phenyl)piperidyl]ethyl((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide.

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The title compound was prepared according to the procedure described in Example 3 (Step b) using *tert*-butyl 3-{(1*R*)-1-[(4-chlorophenyl)methyl]-2-oxo-2-[4-(2-[(2,4,6-trimethylphenyl)sulfonyl]amino)phenyl]piperidyl}ethyl carbamoyl (3*S*)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step a) (146 mg, 0.18 mmol) and 50% TFA in CH₂Cl₂ (10 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (81 mg). MS (ESI, pos. ion) *m/z*: 699 (M+1); (ESI, neg. ion) *m/z*: 697 (M-1). Calc'd for C₃₉H₄₃ClN₄O₄S: 698.27.

15

Example 23



N-[(1*R*)-1-[(4-Chlorophenyl)methyl]-2-(4-(2-[(methylamino)carbonylamino]phenyl)piperidyl)-2-oxoethyl]((3*S*)(3-1,2,3,4-tetrahydroisoquinolyl))-carboxamide

Step (a) *tert*-Butyl 3-{N-[(1*R*)-1-[(4-chlorophenyl)methyl]-2-(4-(2-[(methylamino)carbonylamino]phenyl)piperidyl)-2-oxoethyl]carbamoyl}(3*S*)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

To a 50 mL round-bottomed flask equipped with stirring was added *tert*-butyl 3-{N-[(1*R*)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-

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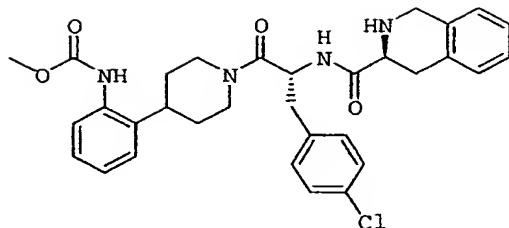
oxoethyl}carbamoyl) (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Example 20) (462 mg, 0.75 mmol) followed by CH₃CN (15 mL) and methylisocyanate (Chemservice, Inc.) (45.6 mg, 0.80 mmol). The reaction mixture was stirred at RT for 5 16 h, then the solvent was removed *in vacuo*. The resulting yellow oil was dissolved in EtOAc (20 mL) and washed with satd NaHCO₃ (20 mL) and satd NaCl (20 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (100% 10 EtOAc) provided the title compound as a white foam (397 mg). MS (ESI, pos. ion) *m/z*: 674 (M+1); MS (ESI, neg. ion) *m/z*: 672 (M-1). Calc'd for C₃₇H₄₄ClN₅O₅: 673.30.

Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[{(methylamino)carbonylamino]phenyl}piperidyl}-2-oxoethyl)({(3S)(3-1,2,3,4-tetrahydroisoquinolyl)})-carboxamide.

The title compound was prepared according to the procedure described in Example 3 (Step b) using *tert*-butyl 20 3-{N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[{(methylamino)carbonylamino]phenyl}piperidyl}-2-oxoethyl)carbamoyl] (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step a) (397 mg, 0.59 mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by reverse phase preparative 25 HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (266 mg). MS (ESI, pos. ion) *m/z*: 574 (M+1); (ESI, neg. ion) *m/z*: 572 (M-1). Calc'd for C₃₂H₃₆ClN₅O₃: 30 573.25. Anal. Calcd for C₃₂H₃₆ClN₅O₃·1.8C₂HF₃O₂: C, 54.86; H, 4.89; N, 8.99. Found: C, 55.11; H, 5.04; N, 9.11.

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Example 24



5

N-((1R)-1-[(4-Chlorophenyl)methyl]-2-{4-[2-(methoxycarbonylamino)phenyl]piperidyl}-2-oxoethyl)((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-carboxamide

10 Step (a) *tert*-Butyl 3-[N-((1R)-1-[(4-chlorophenyl)-methyl]-2-{4-[2-(methoxycarbonylamino)-phenyl]-piperidyl}-2-oxoethyl)carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

To a 50 mL round-bottomed flask equipped with stirring
15 was added *tert*-butyl 3-(N-((1R)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Example 20) (462 mg, 0.75 mmol) and CH₂Cl₂ (15 mL) followed by DIEA (0.16 mL, 0.9 mmol). The reaction
20 mixture was stirred for 5 min at RT then treated with methyl chloroformate (Aldrich) (84.6 mg, 0.9 mmol) at 0°C. The reaction mixture was stirred at RT for 12 h then quenched with satd NaHCO₃ (15 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL).
25 The organic fractions were combined, washed with satd NaCl (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (100% EtOAc) provided the title compound as a white foam (412 mg).

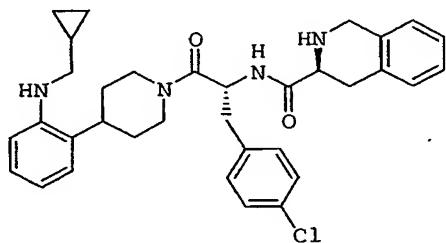
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MS (ESI, pos. ion) *m/z*: 675 (M+1); MS (ESI, neg. ion) *m/z*: 673 (M-1). Calc'd for C₃₇H₄₃ClN₄O₆: 674.29.

Step (b) N-((1R)-1-[(4-Chlorophenyl)methyl]-2-{4-[2-(methoxycarbonylamino)phenyl]piperidyl}-2-oxoethyl)-((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide trifluoroacetate.

The title compound was prepared according to the procedure described in Example 3 (Step b) using *tert*-butyl 3-[N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(methoxycarbonylamino)-phenyl]piperidyl}-2-oxoethyl)-carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step a) (412 mg, 0.61 mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound as a white foam (159 mg). MS (ESI, pos. ion) *m/z*: 575 (M+1); (ESI, neg. ion) *m/z*: 573 (M-1). Calc'd for C₃₂H₃₅ClN₄O₄: 574.23. Anal. Calcd for C₃₂H₃₅ClN₄O₄·1.8C₂HF₃O₂: C, 57.45; H, 5.06; N, 7.75. Found: C, 57.66; H, 5.09; N, 7.62.

Example 25



25

N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-{4-[2-(cyclopropylmethyl)amino]-phenyl}piperidyl]-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide

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Step (a) *tert*-Butyl 3-[N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-(2-[(cyclopropylmethyl)-amino]phenyl)piperidyl)-2-oxoethyl]carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.

5 To a 50 round-bottomed flask equipped with stirring was added *tert*-butyl 3-[N-[(1R)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl]carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Example 20) (462 mg, 0.75 mmol) followed by
10 1,2-dichloroethane (20 mL) and cyclopropyl-carboxaldehyde (Aldrich) (58 mg, 0.83 mmol). The reaction mixture was stirred for 6 h, then treated with sodium triacetoxyborohydride (Aldrich) (176 mg, 0.83 mmol) at 0°C. After stirring for 12 h at RT, the reaction mixture was
15 quenched with satd NaHCO₃ (20 mL). The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 x 20 mL). The organic fractions were combined, washed with satd NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (1:10 MeOH:EtOAc) provided the title compound
20 as a white foam (431 mg). MS (ESI, pos. ion) *m/z*: 671 (M+1); MS (ESI, neg. ion) *m/z*: 669 (M-1). Calcd for C₃₉H₄₇ClN₄O₄: 670.33.

25 **Step (b) N-[(1R)-1-[(4-Chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)amino]-phenyl}piperidyl)-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-carboxamide.**

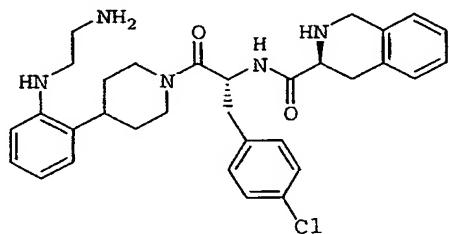
The title compound was prepared according to the
30 procedure described in Example 3 (Step b) using *tert*-butyl 3-[N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(cyclopropylmethyl)-amino]phenyl)piperidyl)-2-oxoethyl]carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step a) (431 mg, 0.64 mmol) and 50% TFA in

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CH_2Cl_2 (20 mL). Purification by reverse phase preparative HPLC [Phenomenex; 5 μm 250 x 21.2 mm, 5% to 95% CH_3CN (0.1% TFA) in H_2O (0.1% TFA) over 30 min, then 100% CH_3CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (207 mg). $^{\text{MS}}$ (ESI, pos. ion) m/z : 571 ($M+1$); (ESI, neg. ion) m/z : 569 ($M-1$). Calc'd for $\text{C}_{34}\text{H}_{39}\text{ClN}_4\text{O}_2$: 570.28. Anal. Calcd for $\text{C}_{34}\text{H}_{39}\text{ClN}_4\text{O}_2 \cdot 2.4\text{C}_2\text{HF}_3\text{O}_2$: C, 55.16; H, 4.94; N, 6.63. Found: C, 55.18; H, 5.13; N, 6.61.

10

Example 26



15 $\text{N}-[(1R)-2-(4-[2-[(2-\text{Aminoethyl})\text{amino}]\text{phenyl}]\text{piperidyl})-1-[(4-\text{chlorophenyl})\text{methyl}]-2-\text{oxoethyl}]((3S)(3-\text{1},2,3,4-\text{tetrahydroisoquinolyl}))\text{carboxamide}$

20 **Step (a) tert-Butyl 3-[N-((1R)-2-[4-[2-[(2-[(tert-butoxy)carbonylamino]ethyl)-amino]phenyl]-piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl]carbamoyl](3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate.**

The title compound was prepared according to the procedure described in Example 25 (Step a) using *tert*-butyl 3-([N-((1R)-2-[4-(2-aminophenyl)piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl]carbamoyl)(3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Example 20) (462 mg, 0.75 mmol), *tert*-butyl N-(2-oxoethyl)carbamate (Aldrich) (131 mg, 0.83 mmol) and NaBH(OAc)_3 (Aldrich) (176 mg, 0.83 mmol) in CH_2Cl_2 (20 mL). Purification by silica gel chromatography (1:10 MeOH:EtOAc) provided the title compound

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as a white foam (386 mg). MS (ESI, pos. ion) *m/z*: 760 (M+1); (ESI, neg. ion) *m/z*: 758 (M-1). Calc'd for C₄₂H₅₄ClN₅O₆: 759.38.

5 **Step (b) N-[(1R)-2-(4-{2-[(2-Aminoethyl)amino]phenyl}piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl] ((3S)(3-1,2,3,4-tetrahydroisoquinolyl)carboxamide.**

The title compound was prepared according to the procedure described in Example 3 (Step b) using *tert*-butyl 10 3-[N-((1R)-2-{4-[2-({2-[(*tert*-butoxy)carbonyl-amino]ethyl}-amino)phenyl}-piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl] (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (Step a) (386 mg, 0.5 mmol) and 50% TFA in CH₂Cl₂ (20 mL). Purification by reverse phase preparative 15 HPLC [Phenomenex; 5 μ m 250 x 21.2 mm, 5% to 95% CH₃CN (0.1% TFA) in H₂O (0.1% TFA) over 30 min, then 100% CH₃CN (0.1% TFA) for 2 min] provided the title compound (TFA salt) as a white foam (162 mg). MS (ESI, pos. ion) *m/z*: 560 (M+1); (ESI, neg. ion) *m/z*: 558 (M-1). Calc'd for C₃₂H₃₈ClN₅O₂: 20 559.27. Anal. Calcd for C₃₂H₃₈ClN₅O₂·3C₂HF₃O₂: C, 50.59; H, 4.58; N, 7.76. Found: C, 50.98; H, 4.87; N, 8.01.

Other compounds included in this invention are set forth in Tables 1-8 below.

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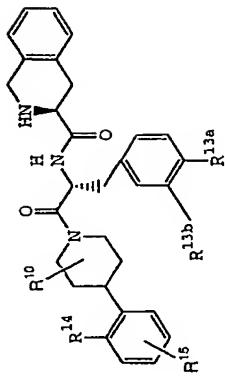
Table 1.

#	R ¹⁴	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
27.	methylsulfonylamino	H	H	C1	H
28.	N-propyl-N-(CypCH ₂) aminomethyl	H	H	C1	H
29.	N-propyl-N-(CypCH ₂) aminomethyl	H	H	Br	H
30.	N,N-di (CypCH ₂) aminomethyl	H	H	C1	H
10	31. N-(methylsulfonyl)-N-(aminoethyl) amino	H	H	C1	C1
	32. methylsulfonylamino	H	3-cypCH ₂ NHC=OCH ₂ -	C1	H
	33. 2-pyridylcarbonylamino	H	H	C1	H
	34. benzylaminocarbonyl	H	H	C1	H
35.		H	H	C1	H
15	36. N-methyl-N-methylcarbonylamino	H	H	C1	H
	37. N-propyl-N-methylsulfonylamino	H	H	C1	H

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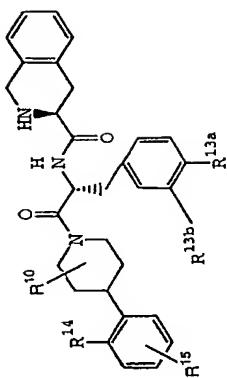
Table 1. cont.

5	#	R ¹⁴	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
	38.	methylsulfonylamino	H	3-NH ₂ -(CH ₂) ₂ NHC=OCH ₂ -	C1	H
	39.	N-(CypCH ₂)-N-(MeSO ₂) aminomethyl	H	H	C1	H
	40.	N-(CypCH ₂)-N-propylaminomethyl	F	H	C1	H
	41.	N-(phenylpropyl)-N-(MeSO ₂) amino	H	H	C1	H
10	42.	methylsulfonylamino	4-CF ₃	H	C1	H
	43.	methylcarbonyl	H	H	C1	H
	44.	N-pyrrolidinylcarbonyl	H	H	C1	H
	45.	CH ₃ C=ONH	H	H	C1	H
	46.	methylsulfonylamino	H	3-phenyl(CH ₂) ₂ NHC=OCH ₂ -	C1	H
15	47.	methoxy	H	H	C1	H
	48.	amino	H	H	C1	H



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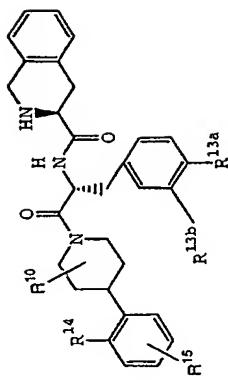
Table 1. cont.



	#	R¹⁴	R¹⁵	R¹⁰	R^{13a}	R^{13b}
	49.	N-(3-pyridylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	50.	N-(isopropylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	51.	N-(pentylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	52.	N-(ethylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
10	53.	N-(t-butylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	54.	N-(butylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	55.	N-(isobutylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	56.	N-(propylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	57.	N-(phenylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	58.	N-(3-methoxyphenylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	59.	N-(benzylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	60.	N-(cyclohexylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
	61.	N-(cyclopentylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H

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Table 1. cont.

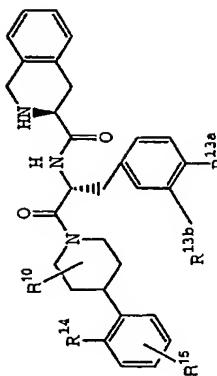


#	R ¹⁴	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
		H	H	C1	H
62.	N-(cyclopropylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
63.	N-(cyclobutylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
64.	N-(2-thienylmethylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
65.	N-(methoxymethylcarbonyl)-N-(aminoethyl) amino	H	H	C1	H
66.	N-(methoxymethylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
67.	N-(methylthiopropyl)-N-(CypCH ₂) amino	H	H	C1	H
68.	N-(methylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
69.	N-(isopropylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
70.	N-(isobutylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
71.	N-(ethylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
72.	N-(3-methoxyphenylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
73.	N-(benzylcarbonyl)-N-(CypCH ₂) amino	H	H	C1	H
74.	N-(phenylethyl)-N-(CypCH ₂) amino	H	H	C1	H

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Table 1. cont.

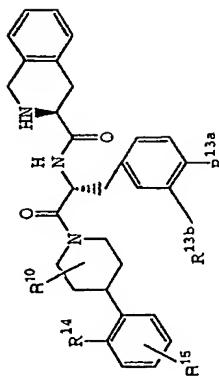
#	R ¹⁴	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
5	75. N- (2-imidazolyl) -N- (CypCH ₂) amino 76. N- (4-methyl-5-imidazolyl) -N- (CypCH ₂) amino 77. N- (4-imidazolylmethyl) -N- (CypCH ₂) amino 78. N- (2-thienylmethyl) -N- (CypCH ₂) amino 79. N- (2-thienylmethylicarbonyl) -N- (CypCH ₂) amino 80. N- (3-furylmethyl) -N- (CypCH ₂) amino 81. N- (phenylcarbonyl) -N- (CypCH ₂) amino 82. N- (cyclopentylcarbonyl) -N- (CypCH ₂) amino 83. N- (cyclohexylcarbonyl) -N- (CypCH ₂) amino 84. N- (cyclopropylcarbonyl) -N- (CypCH ₂) amino 10 15	H H H H H H H H H H H H	H H H H H H H H H H H H	C1 C1 C1 C1 C1 C1 C1 C1 C1 C1 C1 C1	H H H H H H H H H H H H
	85. N- (propyl) -N- (aminoethyl) amino 86. N- (CypCH ₂) -N- (aminoethyl) amino 87. N- (ethyl) -N- (aminoethyl) amino 88. N- (hexyl) -N- (aminoethyl) amino				



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Table 1. cont.

#	R ¹⁴	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
5	89. N- (heptyl) -N- (aminoethyl) amino	H	H	C1	H
	90. N- (butyl) -N- (aminoethyl) amino	H	H	C1	H
	91. N- (3-ethylbutyl) -N- (aminoethyl) amino	H	H	C1	H
	92. N- (2-ethylbutyl) -N- (aminoethyl) amino	H	H	C1	H
	93. N- (phenylethyl) -N- (aminoethyl) amino	H	H	C1	H
10	94. N- (methylsulfonyl) -N- (N', N'-diethylaminoethyl) amino	H	H	C1	H
	95. N- (methylsulfonyl) -N- (N', N'-dipropylaminoethyl) amino	H	H	C1	H
	96. N- (methylsulfonyl) -N- (N', N'-dimethylaminoethyl) amino	H	H	C1	H
	97. N- (methylsulfonyl) -N- (N', N'-di (CypCH ₂) aminoethyl) amino	H	H	C1	H
	98. N-methyl-N- (hydroxyethyl) aminomethyl	H	H	C1	H
15	99. N- (pentyl) -N- (aminoethyl) amino	H	H	C1	H
	100. N,N-di(CypCH ₂) amino	H	H	C1	H
	101. 2-oxo-benzimidazol-1-yl	H	H	C1	H
	102. N- (2-thienylmethylcarbonyl) -N- (CypCH ₂) amino	H	H	C1	H



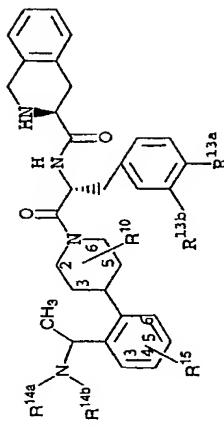
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Table 1. cont.

#	R ¹⁴	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
5		H	H	C1	H
103.	N-(benzylaminocarbonyl)-N-(CypCH ₂) amino				
104.	N-(benzylaminocarbonyl)-N-(aminoethyl) amino	H	H	C1	H
105.	N-(isobutyl)-N-(aminoethyl) amino	H	H	C1	H

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Table 2.

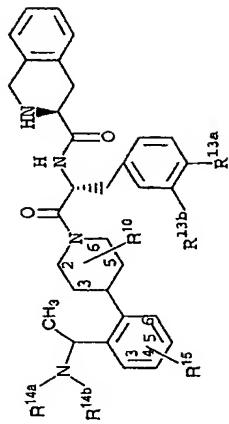


#	R ^{14a}	R ^{14b}	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
106.	cyclopropylmethyl	methyl	H	H	C1	H
107.	cyclopropylmethyl	H	H	H	C1	H
108.	methylcarbonyl	methyl	H	H	C1	H
10	109.	isobutyl	methyl	H	C1	H
	110.	propyl	methyl	H	C1	H
	111.	methylsulfonyl	methyl	H	C1	H
	112.	ethyl	methyl	H	C1	H
	113.	ethoxycarbonylcyclopropylmethyl	methyl	H	C1	H
	114.	isopentyl	methyl	H	C1	H
15	115.	4-methylcarbonylaminobenzyl	methyl	H	C1	H
	116.	methyl	H	4-Br	C1	H
	117.	methyl	methyl	H	C1	H

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Table 2. cont

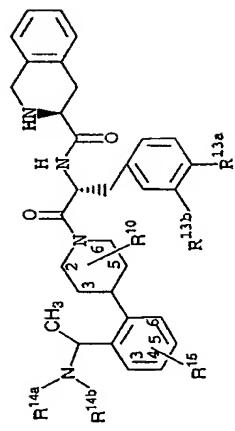
5	#	R ^{14a}	R ^{14b}	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
	118.	3-thienylmethyl	methyl	H	H	C1	H
	119.	benzyloxyethyl	methyl	H	H	C1	H
	120.	2-methoxybenzyl	methyl	H	H	C1	H
10	121.	methyl	H	H	C1	H	H
	122.	4-pyridylmethyl	methyl	H	H	C1	H
	123.	2-pyrrolidinylmethyl	methyl	H	H	C1	H
	124.	3-methoxybenzyl	methyl	H	H	C1	H
	125.	benzyl	methyl	H	H	C1	H
15	126.	aminoethyl	methyl	H	H	C1	H
	127.	4-methoxybenzyl	methyl	H	H	C1	H
	128.	cyclohexylmethyl	methyl	H	H	C1	H
	129.	2-aminopropyl	methyl	H	H	C1	H



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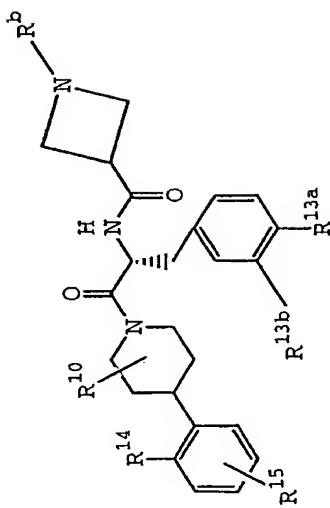
Table 2. cont

5	#	R ^{14a}	R ^{14b}	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}
130.	methylamino		methyl	H	H	C1	H
131.	3-cyanobenzyl		methyl	H	H	C1	H
132.	isopropyl		methyl	H	H	C1	H
10	133. CypCH ₂ -		methylcarbonyl	H	H	C1	H
	134. methylcarbonyl		methyl	H	H	C1	H



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Table 3.

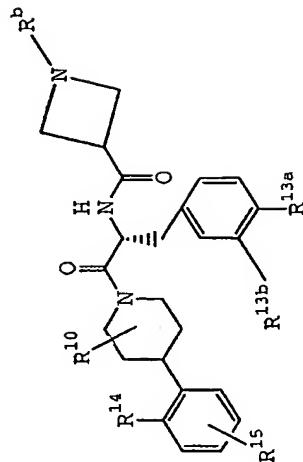


5	#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
	135.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	isobutyl
	136.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	-CH ₂ C(CH ₃) ₃
	137.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	-CH ₂ CYP
10	138.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	butyl
	139.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	pentyl
	140.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	-CH ₂ chx1
	141.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	ethyl
	142.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	methyl
	143.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	isopropyl

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Table 3. cont.

#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
5	144. N- (CH ₃ SO ₂) -N- (CypCH ₂) amino	H	H	C1	H	benzyl
145.	N- (CH ₃ SO ₂) amino	H	H	C1	H	H
146.	N- (CH ₃ SO ₂) -N- (CypCH ₂) amino-	H	H	C1	H	propyl
147.	1,2,3-triazol-2-ylmethyl	H	H	C1	H	H
148.	N-(CypCH ₂) -N-propylaminoCH ₂ -	H	H	C1	H	Boc
10	149. N- (CypCH ₂) -N-propylaminoCH ₂ -	H	H	C1	H	H
150.	1-imidazolylmethyl	H	H	C1	H	H
151.	1-tetrazolylmethyl	H	H	C1	H	H
152.	2,5-dimethylpyrrolidin-1-yl	H	H	C1	H	H
153.	2-oxo-pyrrolidin-5-ylmethyl	H	H	C1	H	H
15	154. 2-oxo-pyrrolidin-1-ylmethyl	H	H	C1	H	isopropyl
155.	2-oxo-pyrrolidin-1-ylmethyl	H	H	C1	H	ethyl



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Table 3. cont.

#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
5	156.	2-oxo-pyrrolidin-1-ylmethyl	H	H	C1	H
	157.	2-oxo-pyrrolidin-1-ylmethyl	H	H	C1	H
	158.	8-aza-bicyclo[3.2.1]oct-8-ylmethyl	H	H	C1	H
	159.	8-aza-bicyclo[3.2.1]oct-8-ylmethyl	H	H	C1	H
	160.	8-aza-bicyclo[3.2.1]oct-8-ylmethyl	H	H	C1	H
10	161.	8-aza-bicyclo[3.2.1]oct-8-ylmethyl	H	H	C1	H
	162.	8-aza-bicyclo[3.2.1]oct-8-ylmethyl	H	H	C1	H
	163.	phenoxyethyl	H	H	C1	H
	164.	1-methylpiperazin-4-ylmethyl	H	H	C1	H
	165.	2,6-dimethylpiperdin-1-ylmethyl	H	H	C1	H
15	166.	3-pyridyloxymethyl	H	H	C1	H
	167.	1,2,3-triazol-2-ylmethyl	H	H	C1	H

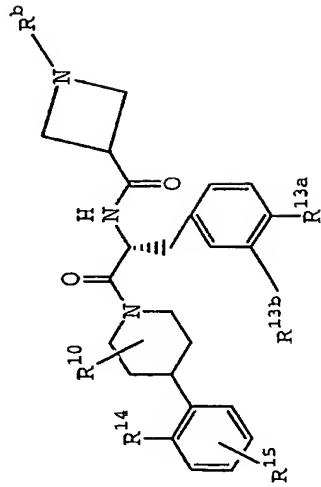
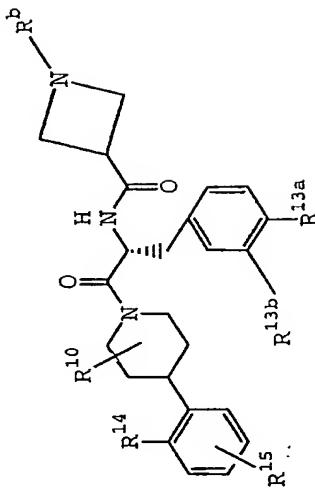
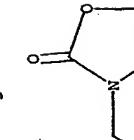


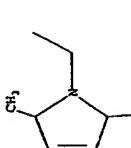
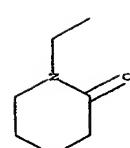
Table 3. cont.



#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
168.	1, 2, 3-triazol-2-ylmethyl	H	H	C1	H	H
5 169.	1, 2, 3-triazol-2-ylmethyl	H	H	C1	H	CyPCH ₂ -
170.	1, 2, 4-triazol-1-ylmethyl	H	H	C1	H	H
171.	2-oxopyridylmethyl	H	H	C1	H	H
172.	1, 2, 3-triazol-2-ylmethyl	H	H	C1	H	isobutyl
173.	4-morpholinomethyl	H	H	C1	H	H
10 174.	2-CH ₃ -imidazol-1-ylmethyl	H	H	C1	H	H
175.		H	H	C1	H	H
176.	2-propylimidazol-1-ylmethyl	H	H	C1	H	H
177.	1-piperidylmethyl	H	H	C1	H	H

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Table 3. cont.

#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
5	178. 1-pyrrolidinylmethyl	H	H	C1	H	H
	179. N-(MeSO ₂)-N-(CypCH ₂) aminomethyl	H	H	C1	H	H
	180. 2-isopropylimidazol-1-ylmethyl	H	H	C1	H	H
	181. 1, 2, 3-triazol-2-ylmethyl	H	H	C1	H	-CH ₂ C(CH ₃) ₃
182.		H	H	C1	H	H
10 183.		H	H	C1	H	H
184.	1, 2, 3-triazol-2-ylmethyl	H	H	C1	H	chx1

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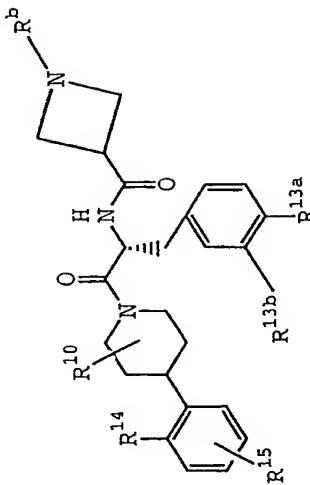
Table 3. cont.

#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
5	185. N-(MeSO ₂)-N-(CypCH ₂) aminomethyl	H	H	C1	H	cycloheptyl
	186. N-(MeSO ₂)-N-(CypCH ₂) aminomethyl	H	H	C1	H	morpholino
	187. N-(MeSO ₂)-N-(CypCH ₂) aminomethyl	H	H	C1	H	2-(ethyl)butyl
	188. N-(MeSO ₂)-N-(CypCH ₂) aminomethyl	H	H	C1	H	chx1
	189. 1-pyrazolylmethyl	H	H	C1	H	CypCH ₂ -
10	190. 1-pyrazolylmethyl	H	H	C1	H	ethyl
	191. 1-pyrazolylmethyl	H	H	C1	H	isopropyl
	192. 1-pyrazolylmethyl	H	H	C1	H	isopropyl
	193. 1,2,3-triazol-1-ylmethyl	H	H	C1	H	isobutyl
	194. N-propyl-N-(CypCH ₂) aminomethyl	H	H	C1	H	ethyl
15	195. N-propyl-N-(CypCH ₂) aminomethyl	H	H	C1	H	-CH ₂ C(CH ₃) ₃
	196. N-(CypCH ₂)-N-propylaminomethyl	H	H	C1	H	

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Table 3. cont.

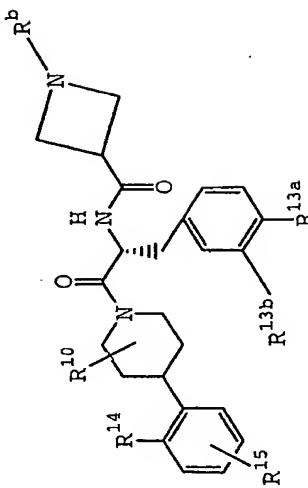
#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
5	197. 1,2,3-triazol-1-ylmethyl	H	H	C1	H	isobutyl
	198. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	isobutyl
	199. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	-CH ₂ C(CH ₃) ₃
	200. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	-CH ₂ cyp
	201. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	butyl
	202. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	pentyl
10	203. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	-CH ₂ chx1
	204. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	ethyl
	205. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	methyl
	206. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	isopropyl
	207. N-(CH ₃ SO ₂)-N-(CypCH ₂) amino	H	H	Br	H	H
	208. N-(CypCH ₂)-N-(MeSO ₂) amino	H	H	C1	H	cyclopentyl
15						



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Table 3. cont.

#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
209.	N-(CYPCH ₂) -N-(MeSO ₂) amino-	H	H	C1	H	2-butyl
5 210.	1, 2, 3-triazol-1-ylmethyl	H	H	C1	H	ethyl
211.	1, 2, 3-triazol-1-ylmethyl	H	H	C1	H	-CH ₂ C(CH ₃) ₃
212.	N-(MeSO ₂) -N-(aminoethyl) amino	H	H	C1	H	H
213.	N-(MeSO ₂) -N-(N', N' -di (methyl) aminoethyl) amino	H	H	C1	H	H
214.	N-(MeSO ₂) -N-(N', N' -di (methyl) aminoethyl) amino	H	H	C1	H	propyl
10 215.	N-(MeSO ₂) -N-(N', N' -di (methyl) aminoethyl) amino	H	H	C1	H	ethyl
216.	N-(MeSO ₂) -N-(N', N' -di (methyl) aminoethyl) amino	H	H	C1	H	methyl
217.	N-(MeSO ₂) -N-(N', N' -di (ethyl) aminoethyl) amino	H	C1	H	H	H
218.	N-(MeSO ₂) -N-(N', N' -di (propyl) aminoethyl) amino	H	H	C1	H	H
219.	N-(MeSO ₂) -N-(N', N' -di (t-butylmethyl) aminoethyl) amino	H	H	C1	H	H
15 220.	N-(MeSO ₂) -N-(N', N' -di (isobutyl) aminoethyl) amino	H	H	C1	H	H



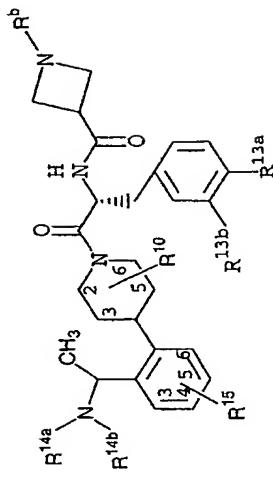
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Table 3. cont.

	#	R ¹⁴	R ¹⁰	R ¹⁵	R ^{13a}	R ^{13b}	R ^b
5	221.	N-(MeSO ₂) -N- (N',N'-di (CypCH ₂) aminoethyl) amino	H	H	C1	H	H
	222.	N-(MeSO ₂) -N- (N',N'-di (2-furylCH ₂) aminoethyl) amino	H	H	C1	H	H
	223.	N-(MeSO ₂) -N- (N',N'-di (2-thienylCH ₂) aminoethyl) amino	H	H	C1	H	H
	224.	N-(MeSO ₂) -N- (N',N'-di (benzyl) aminoethyl) amino	H	H	C1	H	H
	225.	1-methyl-2-oxo-imidazolin-3-yl	H	H	C1	H	H

Table 4.

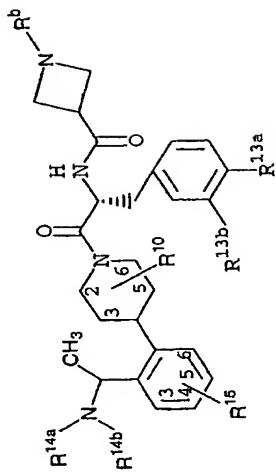
#	R ^{14a}	R ^{14b}	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}	R ^b
226.	cyclopropylmethyl	methyl	H	H	C1	H	H
227.	cyclopropylmethyl	H	H	H	C1	H	H
228.	methylcarbonyl	methyl	H	H	C1	H	CypCH ₂
229.	isobutyl	methyl	H	H	C1	H	H
10	230.	propyl	methyl	H	C1	H	H
	231.	methylsulfonyl	methyl	H	C1	H	H
	232.	ethyl	methyl	H	C1	H	H
	233.	ethoxycarbonylcyclopropylmethyl	methyl	H	C1	H	H
	234.	isopentyl	methyl	H	C1	H	H
15	235.	4-methylcarbonylaminobenzyl	methyl	H	C1	H	H
	236.	methyl	H	4-Br	C1	H	H
	237.	methylcarbonyl	methyl	H	C1	H	isobutyl



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Table 4. cont.

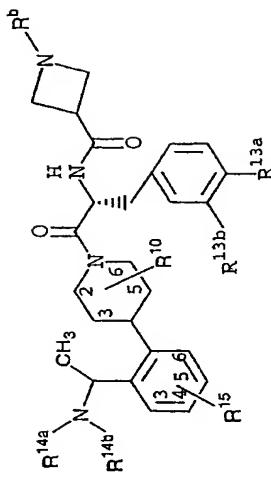
5	#	R ^{14a}	R ^{14b}	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}	R ^b
	238.	methylcarbonyl	methyl	H	H	C1	H	ethyl
	239.	methylcarbonyl	methyl	H	H	C1	H	H
	240.	methylcarbonyl	methyl	H	H	C1	H	isopropyl
10	241.	cyclohexylmethyl	methyl	H	H	C1	H	H
	242.	methyl	methyl	H	H	C1	H	H



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Table 4. cont

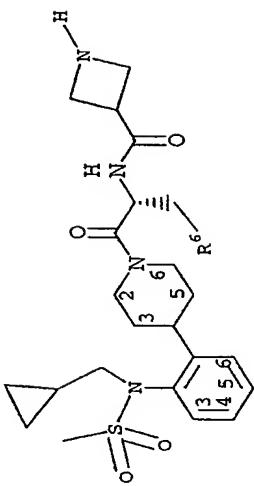
5	#	R ^{14a}	R ^{14b}	R ¹⁵	R ¹⁰	R ^{13a}	R ^{13b}	R ^b
	243.	3-thienylmethyl	methyl	H	H	C1	H	H
	244.	benzyloxyethyl	methyl	H	H	C1	H	H
	245.	2-methoxybenzyl	methyl	H	H	C1	H	H
10	246.	methyl	H	H	C1	H	H	H
	247.	4-pyridylmethyl	methyl	H	H	C1	H	H
	248.	2-pyrrolidinylmethyl	methyl	H	H	C1	H	H
	249.	3-methoxybenzyl	methyl	H	H	C1	H	H
	250.	benzyl	methyl	H	H	C1	H	H
15	251.	aminoethyl	methyl	H	H	C1	H	H
	252.	4-methoxybenzyl	methyl	H	H	C1	H	H



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Table 5.

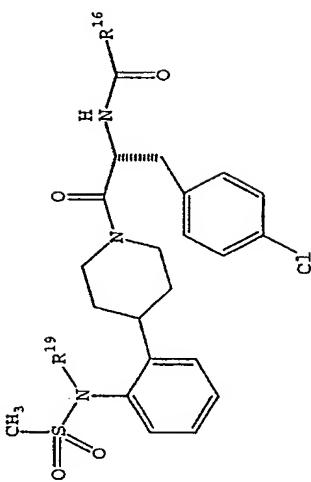
	#	R ⁶
	253.	4-bromophenyl
	254.	2-naphthyl
	255.	1,4-biphenyl
	256.	1-naphthyl
10	257.	3,4-dichlorophenyl
	258.	4-methoxyphenyl
	259.	4-iodophenyl
	260.	3-chlorophenyl
	261.	4-trifluoromethylphenyl
15	262.	3-pyridyl



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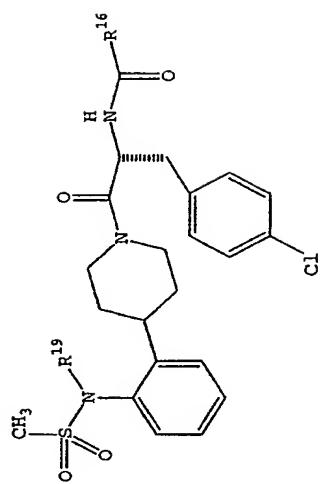
Table 6

#	R ¹⁹	R ¹⁶
263.	-CH ₂ CYP	6-quinolyl
5 264.	-CH ₂ CYP	4-(benzyl oxy) phenyl
265.	-CH ₂ CYP	-CH ₂ CH ₂ NHCH ₃
266.	-CH ₂ CYP	3, 4-dimethoxyphenyl
267.	-CH ₂ CYP	4-(phenoxy) phenyl
268.	-CH ₂ CYP	-CH ₂ CH ₂ NH ₂
10 269.	-CH ₂ CYP	4-piperidyl
270.	-CH ₂ CYP	4-fluorophenyl
271.	-CH ₂ CYP	4-(1-pyrrolyl) phenyl
272.	-CH ₂ CYP	5-methoxyindol-2-yl
273.	-CH ₂ CYP	3-quinolyl



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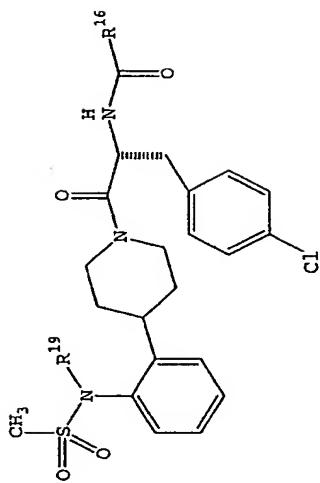
Table 6 cont.



#	R ¹⁹	R ¹⁶
274.	-CH ₂ Cyp	3-cyanophenyl
5 275.	-CH ₂ Cyp	4-(1-isobutyl)piperidyl
276.	-CH ₂ Cyp	4-(1-ethyl)piperidyl
277.	propyl	3-fluorophenyl-CH ₂ -
278.	-CH ₂ Cyp	3-methoxyphenyl
279.	propyl	2-CF ₃ -phenyl-CH ₂ -
10 280.	-CH ₂ Cyp	2-methylthiophenyl
281.	-CH ₂ Cyp	-CH(Me)phenyl
282.	-CH ₂ Cyp	3,4-dimethoxyphenyl-CH ₂ CH ₂
283.	-CH ₂ Cyp	3-fluorophenyl
284.	-CH ₂ Cyp	4-pyridyl

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Table 6 cont.

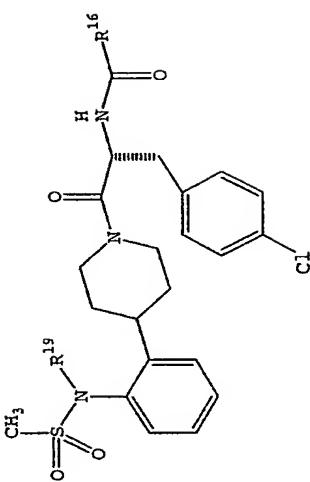


#	R^{19}	R^{16}
285.	- CH_2CYP	4-(1-methyl)piperidyl
5 286.	- CH_2CYP	3-(aminomethyl)phenyl
287.	- CH_2CYP	2-methylthio pyrid-3-yl
288.	- CH_2CYP	1-aminochxyl
289.	- CH_2CYP	(1-phenyl)aminomethyl
290.	- CH_2CYP	3-tetrahydrofuranyl
10 291.	- CH_2CYP	2-thienyl
292.	- CH_2CYP	2-indolyl
293.	- CH_2CYP	cyclohexyl
294.	- CH_2CYP	1-aminoethyl
295.	- CH_2CYP	3-piperidyl

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Table 6 cont.

#	R ¹⁹	R ¹⁶
296.	-CH ₂ CYP	phenyl
5 297.	-CH ₂ CYP	4-chlorophenyl
298.	-CH ₂ CYP	2-(4-pyridyl)oxazolyl
299.	propyl	3-fluorophenyl
300.	propyl	2-fluorophenyl
301.	-CH ₂ CYP	2-naphthyl
10 302.	-CH ₂ CYP	3-indolyl
303.	-CH ₂ CYP	3-pyridyl
304.	-CH ₂ CYP	3-isquinolyl
305.	-CH ₂ CYP	1-methylcyclopropyl
306.	-CH ₂ CYP	2-chlorophenyl



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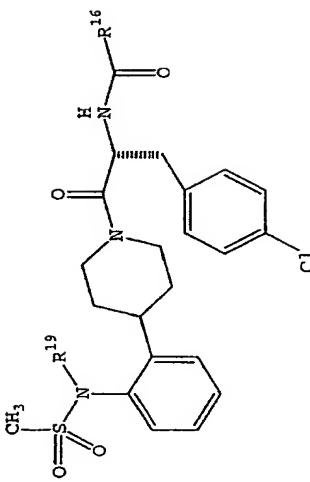
Table 6 cont.

#	R ¹⁹	R ¹⁶
307.	-CH ₂ Cyp	phenyl(1-amino)ethyl
5 308.	-CH ₂ Cyp	2-(1,2,3,4-tetrahydronaphthyl)
309.	-CH ₂ Cyp	phenyl-HC=C(CH ₃)-
310.	-CH ₂ Cyp	isopropyl
311.	-CH ₂ Cyp	phenyl-CH(CH ₃)CH ₂ -
312.	-CH ₂ Cyp	phenyl(1-hydroxy)ethyl
10 313.	-CH ₂ Cyp	3-indolylethyl
314.	propyl	2-fluorophenylethyl
315.	-CH ₂ Cyp	1-phenoxypropyl
316.	-CH ₂ Cyp	-CH ₂ C(CH ₃) ₃
317.	propyl	1-(4-fluoronaphthyl)
15		

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Table 6 cont.

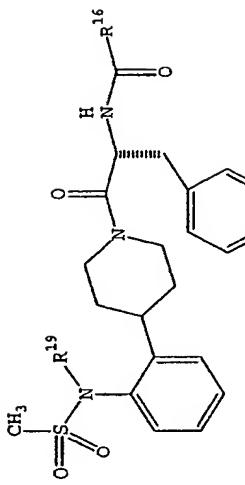
#	R ¹⁹	R ¹⁶
318.	H	4-aminochx1
5 319.	-CH ₂ CYP	2-benzothienyl
320.	-CH ₂ CYP	2-(1-methylindolyl)
321.	-CH ₂ CYP	5-(4-chloro-1,3-dimethyl)pyridylpyrazolyl
322.	-CH ₂ CYP	2-indanylCH ₂ -
323.	H	3-aminocyclopentyl-
10 324.	H	5-indolyl
325.	-CH ₂ CYP	phenyl(1-methylamino)ethyl
326.	-CH ₂ CYP	3-indolylCH ₂ -
327.	H	1-methyl-pyrrolidin-5-yl
328.	H	3-phenyl-2-pyrrolidinyl
15 329.	-CH ₂ CYP	2-(7-pyridyl)oxazolyl



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Table 6 cont.

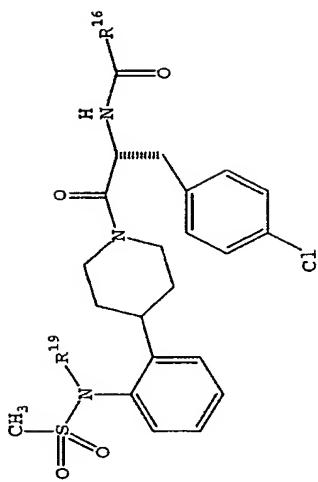
#	R ¹⁹	R ¹⁶
330.	-CH ₂ CYP	2-benzoxazolyl
5 331.	-CH ₂ CYP	2-methoxyphenyl
332.	-CH ₂ CYP	3-(phenoxy)phenyl
333.	-CH ₂ CYP	2-benzofuran
334.	H	3-pyridylethyl
335.	H	1-methyl-5-pyridyl-2-oxo-pyrrolidin-4-yl
10 336.	-CH ₂ CYP	4-dimethylaminophenyl-CH ₂ -
337.	propyl	(2,5-di-trifluoromethylphenyl)ethyl
338.	-CH ₂ CYP	2-methyl-3-indolyl
339.	-CH ₂ CYP	1-(benzylamino)ethyl
340.	H	2-(4-pyridyloxazolyl)



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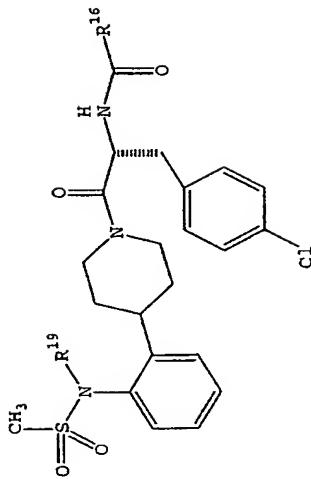
Table 6 cont.

#	R ¹⁹	R ¹⁶	
5	341. 342. 343. 344. 345. 10 346. 347. 348. 349. 350. 15 351.	H propyl CypCH ₂ - CypCH ₂ - CypCH ₂ - propyl propyl CypCH ₂ - CypCH ₂ - propyl propyl	2-quinolyl 4-piperidyl 4-ethoxycarbonylpiperid-1-yl 1-piperaziny1 4-Boc-piperid-1-yl 3-CF ₃ -phenyl 4-CF ₃ -phenyl 3-CF ₃ -phenyl 4-CF ₃ -phenyl 4-fluorophenyl 2-naphthyl



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Table 6 cont.



#	R ¹⁹	R ¹⁶
352.	propyl	phenyl
5 353.	propyl	3-pyridyl
354.	propyl	4-pyridyl
355.	CypCH ₂ -	4-pyridyl
356.	CypCH ₂ -	4-(benzyl)phenyl
357.	CypCH ₂ -	4-(phenylamino)phenyl
10 358.	CypCH ₂ -	2-(cyclopentyl)-1-(phenyl)methyl
359.	CypCH ₂ -	1-(cyclopentyl)-1-(phenyl)methyl
360.	CypCH ₂ -	4-(tert-butyl)phenyl
361.	CypCH ₂ -	1-methyl-2-indolyl
362.	CypCH ₂ -	5-nitro-3-phenyl-2-indolyl
15 363.	CypCH ₂ -	4-chloro-1,3-dimethyl-1H-pyrazolo[3,4-b]pyrid-6-yl

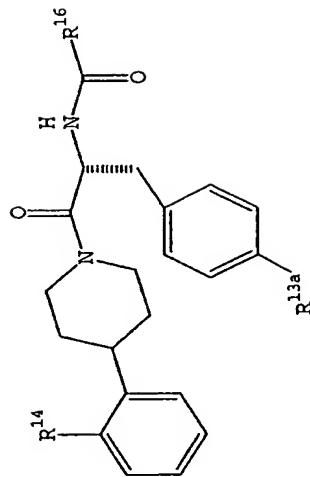
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Table 6 cont.

#	R ¹⁹	R ¹⁶
364.	CypCH ₂ -	2-(4-chlorophenoxy)-2-methylethyl
365.	CypCH ₂ -	3-chlorophenyl
366.	H	1-methyl-2-pyrrolyl
367.	H	2-oxo-1-pyrrolyl
368.	H	2-oxo-5-pyrrolyl
369.	CypCH ₂ -	

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Table 7.

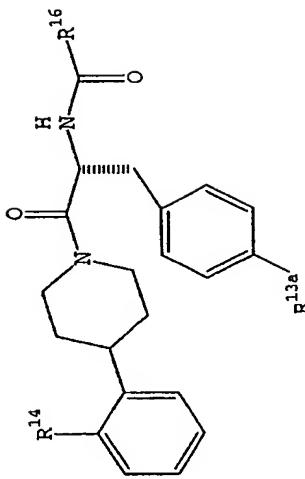


#	R ¹⁴	R ¹⁶	R ^{13a}
370.	1- (N- (CypCH ₂) amino) ethyl	6-quinolyl	C1
5 371.	1- (N, N- (CypCH ₂) ₂ amino) ethyl	6-quinolyl	C1
372.	1- (N- (CypCH ₂) -N-propylamino) ethyl	6-quinolyl	C1
373.	(N, N- (CypCH ₂) ₂ amino) CH ₂ -	6-quinolyl	C1
374.	N- (CypCH ₂) -N-propylaminomethyl	6-quinolyl	C1
375.	N- (CypCH ₂) -N-ethylaminomethyl	6-quinolyl	C1
10 376.	N, N- (propyl) aminomethyl	6-quinolyl	C1
377.	1- (N- (CypCH ₂) -N-butylamino) ethyl	6-quinolyl	C1
378.	1- (N-CypCH ₂) -N-isopentylamino) ethyl	6-quinolyl	C1
379.	1- (N- (CypCH ₂) -N- (Chx1CH ₂) amino) ethyl	6-quinolyl	C1
380.	1- (N- (CypCH ₂) -N- (CH ₃ S(CH ₂) ₃) amino) ethyl	6-quinolyl	C1
15 381.	N- (CypCH ₂) -N- (MeSO ₂) aminomethyl	6-quinolyl	C1

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Table 7. cont.

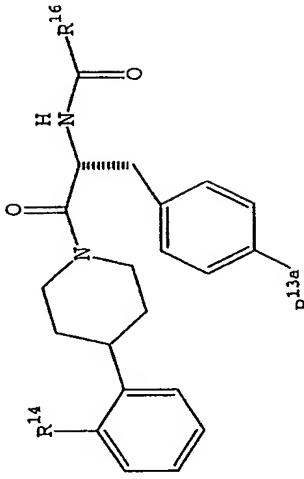
	#	R ¹⁴	R ¹⁵	R ^{13a}
5	382.	1-(N-(CypCH ₂)-N-(3-thienylmethyl) amino) ethyl	6-quinolyl	C1
	383.	1-(N-(CypCH ₂)-N-(CH ₃ C=O) amino) ethyl	6-quinolyl	C1
	384.	1-hydroxyethyl	6-quinolyl	C1
	385.	1-(N-(CypCH ₂)-N-isobutylamino) ethyl	6-quinolyl	C1
10	386.	1-(N-(CypCH ₂)-N-(phenylethyl) amino) ethyl	6-quinolyl	C1
	387.	N-(CypCH ₂)-N-(MeSO ₂) aminomethyl	6-quinolyl	C1
	388.	1-(N-(CypCH ₂)-N-(pentyl) amino) ethyl	6-quinolyl	C1
	389.	N,N-di(isobutyl) aminomethyl	6-quinolyl	C1
15	390.	1-(N-(CypCH ₂)-N-(2-ethylbutyl) amino) ethyl	6-quinolyl	C1
	391.	1-(N-(CypCH ₂)-N-(3-methylphenyl) amino) ethyl	6-quinolyl	C1
	392.	N-(MeSO ₂)-N-(CypCH ₂) aminomethyl	3-isooquinolyl	C1
	393.	1-(N-(CypCH ₂) amino) ethyl	3-isooquinolyl	C1



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Table 7. cont.

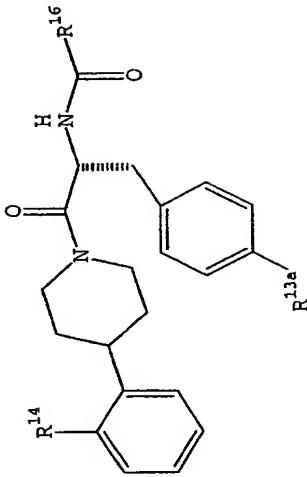
#	R ¹⁴	R ¹⁶	R ^{13a}
394.	N-(MesO ₂)-N-(CypCH ₂)aminomethyl	4-piperidyl	C1
5	N-propyl-N-(CypCH ₂)aminomethyl	piperid-1-ylethyl	C1
395.	1,2,3-triazol-1-ylmethyl	1-ethylpiperid-4-yl	C1
396.	N-propyl-N-(CypCH ₂)aminomethyl	1-isobutylpiperid-4-yl	C1
397.	N-isopropyl-N-(CypCH ₂)aminomethyl	1-ethylpiperid-4-yl	C1
398.	N-ethyl-N-(CypCH ₂)aminomethyl	1-ethylpiperid-4-yl	C1
399.	N-ethyl-N-(CypCH ₂)aminomethyl	1-ethylpiperid-4-yl	C1
10	N-cyclopentyl-N-(CypCH ₂)aminomethyl	1-ethylpiperid-4-yl	C1
400.	1,2,3-triazol-1-ylmethyl	1-isopropylpiperid-4-yl	C1
401.	1,2,3-triazol-1-ylmethyl	1-(CypCH ₂)piperid-4-yl	C1
402.	1,2,3-triazol-1-ylmethyl	1-isobutylpiperid-4-yl	C1
403.	1,2,3-triazol-1-ylmethyl	1-[(CH ₃) ₃ CCH ₂]piperid-4-yl	C1
404.	1,2,3-triazol-1-ylmethyl	6-quinolyl	Br
15	N-(CypCH ₂)-N-propylaminomethyl		



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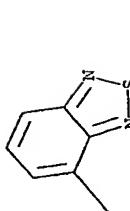
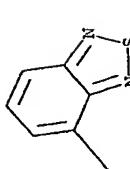
Table 7. cont.

#	R ¹⁴	R ¹⁶	R ^{13a}
5	406. N-(CypCH ₂) -N-propylaminomethyl	3-quinolyl	Br
	407. N-(CypCH ₂) -N-propylaminomethyl	4-piperidyl	Br
	408. N-(CypCH ₂) -N-propylaminomethyl	1-ethylpiperid-4-yl	Br
	409. N-propyl-N-(CypCH ₂) aminomethyl	1-isobutylpiperid-4-yl	Br
	410. N-(CypCH ₂) -N-propylaminomethyl	1-isopropylpiperid-4-yl	Br
10	411. N-(CypCH ₂) -N-propylaminomethyl	1-(CypCH ₂) piperid-4-yl	Br
	412. N-(CypCH ₂) -N-propylaminomethyl	1-isobutylpiperid-4-yl	Br
	413. N-(CypCH ₂) -N-propylaminomethyl	1-[(CH ₃) ₃ CCH ₂) piperid-4-yl	Br
	414. N-(CypCH ₂) -N-propylaminomethyl	piperid-1-ylethyl	Br
	415. N-(CypCH ₂) -N-propylaminomethyl	ethylaminoethyl	Br
15	416. 1-(N-(CypCH ₂) amino) ethyl	2-quinolyl	C1
	417. 1-(N-(CypCH ₂) amino) ethyl	4-piperidyl	C1



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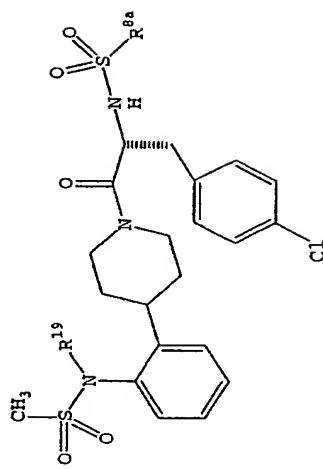
Table 8

#	R ¹⁹	R ^{3a}	
5	418. -CH ₂ CYP 419. -CH ₂ CYP 420. -CH ₂ CYP 421. -CH ₂ CYP 422. -CH ₂ CYP 423. -CH ₂ CYP 424. -CH ₂ CYP 425. -CH ₂ CYP 426.		
10	-CH ₂ CYP		1-methylimidazol-4-yl
			3,5-dimethylisoxazol-4-yl
			2-methoxycarbonylthien-3-yl
			4-fluorophenyl
			4-methylcarbonylaminophenyl
			2-(phenylcarbonylaminomethyl)thien-5-yl

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Table 8

#	R ¹⁹	R ^{8a}
427.	-CH ₂ CYP	1-naphthyl
428.	-CH ₂ CYP	6-quinolyl
5	-CH ₂ CYP	2-(trifluoromethylcarbonyl)-1,2,3,4-tetrahydroisoquinol-7-yl
429.	-CH ₂ CYP	



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Although the pharmacological properties of the compounds of Formula I vary with structural change, in general, activity possessed by compounds of Formula I may be demonstrated *in vivo*. The pharmacological properties of the 5 compounds of this invention may be confirmed by a number of pharmacological *in vitro* assays. The exemplified pharmacological assays which follow have been carried out with the compounds according to the invention and their salts.

10

BIOLOGICAL EVALUATION

A number of models exist for the study of obesity (see, e.g., Bray, G. A., 1992, *Prog. Brain Res.* 93: 333-341; 15 and Bray, G.A., 1989, *Amer. J. Clin. Nutr.* 5: 891-902). Animals having mutations which lead to syndromes that include obesity symptoms have also been identified.

Attempts have been made to utilize such animals as models for the study of obesity, and the best studied animal 20 models to date for genetic obesity are mice. For reviews, see, e.g., Friedman, J.M. et al., 1991, *Mamm. Gen.* 1: 130-144; Friedman, J.M. and Liebel, R.L., 1992, *Cell* 69: 217-220.

Assays which demonstrate MCR4/MCR3 agonistic activity 25 of compounds are well known in the art. One particularly useful assay is the BioTrak TM cAMP direct enzyme immunoassay (EIA) system from Amersham Pharmacia Biotech, which quantitates the cAMP response of cells to MC ligands. This system allows the simple quantitation of total cellular 30 cAMP measurement in cells exposed to selective ligands. Briefly summarized: HEK cells stably transfected with the MC-1, MC-3 or MC-4 receptors are plated into 96 well microtiter plates and grown overnight. Cells are dosed with the appropriate MC ligand for 1 hour and then lysed. A

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fraction of the lysed cell extract is transferred to the assay plate. The ELISA assay is performed according to kit instructions. Each plate contains a series of cAMP standards for calculating a standard curve, as well as a full MC
5 agonist as a positive control for each MC receptor. cAMP activity is calculated as a % of the maximum cAMP activity of the full MC agonist control.

Penile erection test in the rat

10

Method that can be used includes a modified version of that reported by Heaton et al. (J. Urol., 145, 1099-1102, 1991.) and Ghazi-Kanzari et al. (Pharmacol. Toxicol., 81, 81-84, 1997.). Rats are kept under a reversed 12-hr
15 light/dark cycle for 5 days prior to testing. On the test day, animals are administered compound via intraperitoneal route of administration 1 hr after the lights go off and then immediately placed in individual Plexiglas cages (32 x 14 x 13 cm). Under red lighting, rats are observed for 1
20 hr. The number of penile erections and yawns are recorded. There are 10 animals per treatment group and bromocriptine (4 mg/kg) is used as the reference agent as well as a vehicle control. Data are analyzed by comparing treated groups with vehicle control using Mann Whitney U tests.
25

Fast-induced food intake in mice

Male C57BL/6 mice (25-30 g) were used for studies. Food was removed from group-housed mice (5-8/cage) overnight
30 (16-18 hr). The next day, mice were dosed with compound (in 20% Captisol or HPMC/Tween or PBS, depending on the solubility) and then placed into individual cages. Fifteen min following systemic dosing or 30 min following intracerebroventricular (i.c.v) dosing (i.e., time to

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recover from anesthesia), a pre-weighed amount of food was placed in each cage. Food was then weighed 1, 2 and 4 hr after replacement. Cumulative food intake was determined as the difference between the initial weight of the food and
5 the weight of the food at each time point. For statistical analysis, food intake values of compound treated animals were compared with that of vehicle treated animals using ANOVA followed by a post-hoc test (i.e., FLSD) when warranted. For these studies, group sizes for each
10 treatment were 8-10 animals. For i.c.v. dosing, animals were anesthetized using isoflurane. Next, the i.c.v. injection was made using a free-hand technique. Mice were allowed 30 min to recover prior to the start of the test.

Examples 11, 12 and 16 caused a reduction in feeding
15 at concentrations of 30 mg/kg or below.

Formulations

In practical use, the compounds of Formula I can be
20 combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral
25 (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such
30 as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard

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and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Also embraced within this invention is a class of 5 pharmaceutical compositions comprising the active compounds of Formula I in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The 10 active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended.

The compounds and compositions of the present 15 invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, nasal or buccal or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion 20 techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this 25 invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For example, in the case of a 70 kg adult human, these 30 may contain an amount of active ingredient from about 0.7 to 3500 mg, preferably from about 5 to 1500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

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The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and
5 medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about
10 0.01 to 100 mg/kg body weight, preferably between about 0.1 and about 50 mg/kg body weight and most preferably between about 0.5 to 20 mg/kg body weight, may be appropriate may be appropriate. The daily dose can be administered in one to four doses per day.

15 For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient.
20 Examples of such dosage units are tablets or capsules.

Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and
25 mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit
30 form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these

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compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an
5 effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more
10 adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium
15 and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be
20 provided in a dispersion of active compound in hydroxypropylmethyl cellulose for the treatment of sexual dysfunction compounds of the present invention can be given orally or as a nasal spray.

In the case of skin conditions, it may be preferable
25 to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions,
30 ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical

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administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably 5 from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If 10 desired, the aqueous phase of the cream base may include, for example at Least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which 15 enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The compounds of this invention can also be 20 administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a 25 membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the 30 encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or

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an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, 5 the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable 10 for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

15 The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably 20 be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl 25 myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft 30 paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier,

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especially an aqueous solvent for the active ingredients.

The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

5 Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for
10 use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol,
15 sodium chloride, tragacanth gum, and/or various buffers.
Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline,
20 dextrose, or water, or with cyclodextrin (i.e. Captisol), cosolvent solubilization (i.e. propylene glycol) or micellar solubilization (i.e. Tween 80).

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic
25 parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as
30 a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

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For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug
5 can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

10 The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can
15 additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For
20 instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

25 The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended
30 claims.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope

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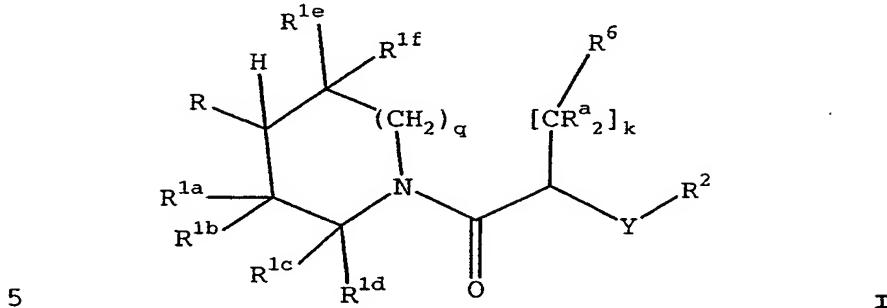
thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their 5 entirety, as if here written.

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WHAT IS CLAIMED IS:

1. A compound of Formula I



wherein Y is -NH-, -CH₂-, or -O-;

wherein R is selected from

- a) alkyl,
 - b) $-(\text{CH}_2)_n$ -cycloalkyl,
 - c) $-(\text{CH}_2)_n$ -aryl, and
 - d) $-(\text{CH}_2)_n$ -heterocyclyl;

wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the

15 heterocyclyl group is optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl group is optionally substituted with 1 to 3 groups selected from R⁵;

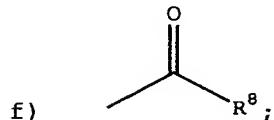
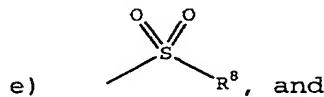
wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are independently selected from R⁴; or wherein R^{1a} and R^{1b} or R^{1d} and R^{1c} form oxo; or wherein R^{1e} and R^{1c} form an alkyleneyl or alkenyleneyl bridge; or wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d} together with the piperazine ring forms an optionally substituted 1,2,3,4-tetrahydro-quinoxalinyl ring;

25 wherein R^2 is selected from

- a) alkyl,
 - b) $-(\text{CH}_2)_n$ -cycloalkyl,
 - c) $-(\text{CH}_2)_n$ -aryl,

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d) $-(\text{CH}_2)_n$ -heterocyclyl,



5 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl group is optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl group is optionally substituted with 1 to 3 groups selected from R⁵;

10 wherein R³ is independently selected from H, halo, amino, haloalkyl, alkyl, phenyl, haloalkoxy, and alkoxy; or wherein R³ is an alkenylene bridge;

15 wherein R⁴ is selected from H, alkyl, $-(\text{CH}_2)_n$ -cycloalkyl, $-(\text{CH}_2)_n$ -aryl, $-(\text{CH}_2)_n$ -heterocyclyl, halo, $-(\text{CH}_2)_n$ -OR⁹, $-\text{NR}^9\text{SO}_2\text{R}^7$, $-[\text{C}(\text{R}^7)_2]_p\text{NR}^9\text{SO}_2\text{R}^7$, $-[\text{C}(\text{R}^7)_2]_p\text{NR}^9\text{C(O)R}^7$, $-\text{N}(\text{R}^9)_2$, $-\text{C(O)NR}^9\text{R}^9$, $-\text{NR}^9\text{C(O)R}^7$, $-\text{NR}^9\text{CO}_2\text{R}^7$, cyano, $-\text{COOR}^9$, $-(\text{CH}_2)_n\text{C=OR}^7$, $-(\text{CH}_2)_n\text{C=SR}^7$, $-(\text{CH}_2)_n\text{C=(NR}^9\text{)R}^7$, $-\text{NR}^9\text{C=(NR}^7\text{)N(R}^9\text{)}_2$, $-\text{[C}(\text{R}^7)_2]_p\text{N(R}^9\text{)}_2$, nitro, $-\text{SO}_2\text{N(R}^9\text{)}_2$, $-\text{S(O)}_m\text{R}^7$, $-\text{C}(\text{R}^7)_2\text{SO}_2\text{CF}_3$,

20 hydroxyalkyl, haloalkyl and haloalkoxy;

wherein R⁵ is selected from halo, $-\text{OR}^9$, NHSO_2R^7 , $-\text{N}(\text{R}^9)_2$, cyano, $-\text{COR}^7$, $-\text{[C}(\text{R}^7)_2]_n\text{N(R}^9\text{)}_2$, nitro, $-\text{SO}_2\text{N(R}^9\text{)}_2$, $-\text{S(O)}_m\text{R}^7$, haloalkyl, and haloalkoxy;

25 wherein R⁶ is selected from aryl and heteroaryl, wherein R⁶ is optionally substituted with one or more R³;

wherein R⁷ is selected from H, alkyl, $-(\text{CH}_2)_n$ -cycloalkyl, $-(\text{CH}_2)_n$ -heterocyclyl, $-(\text{CH}_2)_n$ -aryl, aminoalkyl, alkylamino, alkenyl, alkylcarbonylaminoalkyl, alkylthioalkyl, alkylaminoalkyl, alkoxyalkyl and alkoxy;

30 wherein R⁸ is selected from

a) heterocyclyl,

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- b) aminoalkyl,
- c) aminoalkylamino,
- d) alkylaminoalkylamino,
- e) alkylaminoalkyl,
- 5 f) arylaminoalkyl,
- g) arylalkylaminoalkyl,
- h) heterocyclalkylaminoalkyl,
- i) aryl,
- j) alkyl,
- 10 k) aralkyl,
- l) heterocyclalkyl,
- m) cycloalkylalkyl,
- n) -OR⁹
- o) aminoalkoxy,
- 15 p) N-(heterocyclalkyl)amino,
- q) aralkyl where the alkyl portion is substituted with amino, hydroxy or alkylamino, and
- r) heterocyclalkylenyl where the alkylene portion is substituted with amino, hydroxy or alkylamino;
- 20 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocycl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl groups are optionally substituted with 1 to 3 groups selected from R⁵;
- 25 wherein R⁹ is selected from H, alkyl, alkenyl, cycloalkyl-(CH₂)_n-, heterocycl-(CH₂)_n-, aryl-(CH₂)_n-, aminoalkyl, alkylcarbonylaminoalkyl, cycloalkylaminoalkyl, cycloalkylalkylaminoalkyl, heteroarylarninoalkyl,
- 30 heteroarylalkylaminoalkyl, arylaminoalkyl, arylalkylaminoalkyl, heteroaryloxyalkyl, heteroarylalkyloxyalkyl, arylalkyloxyalkyl, aryloxyalkyl, alkylthioalkyl, alkylaminoalkyl, hydroxyalkyl and alkoxyalkyl;

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wherein R^a are independently selected from H, and alkyl or
the two R^a's together form cycloalkyl;
wherein k is 0 or 1;
wherein m is 0, 1 or 2;
5 wherein n is 0, 1, 2, 3 or 4;
wherein p is 1 or 2; and
wherein q is 1 or 2;
provided R⁶ is not ortho-substituted; further provided R⁶ is
not thienyl or 3-indolyl; further provided R² is not
10 unsubstituted 5-membered saturated or partially
unsaturated heterocyclyl; further provided R is ortho
substituted with R⁴ when n is 0 and when R is -(CH₂)_n-
aryl; further provided R is not unsubstituted 2-
pyrimidinyl, or benzodioxolylmethyl; and further provided
15 R² is not -(C=O)oxiranyl;
and a pharmaceutically-acceptable salt thereof.

2. Compound of Claim 1 wherein Y is -NH- or -CH₂-;
wherein R is selected from
20 a) -(CH₂)_n-C₃₋₈-cycloalkyl,
b) aryl
c) unsubstituted benzyl, and
d) -(CH₂)_n-5-6-membered heterocyclyl;
wherein R is substituted at the 2-position of the
25 cycloalkyl, heterocyclyl, benzyl and aryl groups with a
radical selected from R⁴; and wherein the cycloalkyl and
aryl groups are optionally substituted with 1 to 2
additional radicals selected from R⁴; and the
heterocyclyl group is optionally substituted with 1 to 2
30 additional radicals selected from R⁴ and oxo;
wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are independently
selected from R⁴; or wherein R^{1a} and R^{1b} or R^{1d} and R^{1c} form
oxo; or wherein R^{1e} and R^{1c} form an C₁₋₄-alkylenyl or C₂₋₄-
alkenylenyl bridge; or wherein R^{1a}, R^{1b}, R^{1c}, and R^{1d}

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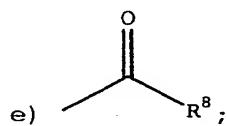
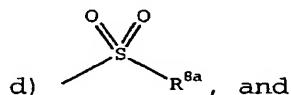
together with the piperazine ring forms an optionally substituted 1,2,3,4-tetrahydro-quinoxaliny1 ring;

wherein R² is selected from

a) -(CH₂)_n-C₃₋₈-cycloalkyl,

5 b) -(CH₂)_n-aryl,

c) -(CH₂)_n-4-10-membered heterocyclyl,



10 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; and the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo;

wherein R³ is independently selected from H, halo, amino, C₁₋

15 C₆-haloalkyl, C₁₋₆-alkyl, phenyl, C₁₋₆-haloalkoxy and C₁₋₆-alkoxy; or wherein R³ is an C₂₋₄-alkenylene bridge;

wherein R⁴ is selected from H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₆-

cycloalkyl, -(CH₂)_n-aryl, -(CH₂)_n-4-10-membered

heterocyclyl, halo, -(CH₂)_n-OR⁹, -NR⁹SO₂R⁷, -N(R⁹)₂, -

C(O)NR⁹R⁹, -NR⁹C(O)R⁷, -NR⁹CO₂R⁷, nitro, cyano, -(CH₂)_n-

C(O)R⁷, -C(O)OR⁹, -(CH₂)_n-C(S)R⁷, -(CH₂)_n-C=(NR⁹)R⁷, -

NR⁹C=(NR⁷)N(R⁷)₂, -[C(R⁷)₂]_pNR⁹SO₂R⁷, -[C(R⁷)₂]_pNR⁹C(O)R⁷, -

[C(R⁷)₂]_pN(R⁹)₂, -SO₂N(R⁹)₂, -S(O)_mR⁷, -C(R⁷)₂SO₂CF₃, C₁₋₆-

hydroxyalkyl, C₁₋₆-haloalkyl and C₁₋₆-haloalkoxy;

25 wherein R⁵ is selected from halo, -OR⁹, -NHSO₂R⁷, -N(R⁹)₂, cyano, -COR⁷, -]C(R⁷)₂]_nN(R⁹)₂, nitro, -SO₂N(R⁹)₂, -S(O)_mR⁷,

C₁₋₆-haloalkyl and C₁₋₆-haloalkoxy;

wherein R⁶ is selected from phenyl, naphthyl and 6-membered heteroaryl, wherein R⁶ is optionally substituted with one

30 or more R³;

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wherein R⁷ is selected from H, C₁₋₆-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl, -(CH₂)_n-phenyl, amino-C₁₋₆-alkyl, C₁₋₆-alkylamino, C₂₋₆-alkenyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, 5 C₁₋₆-alkylamino-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl and C₁₋₆-alkoxy;

wherein R⁸ is selected from

- a) 4-10-membered heterocyclyl,
- b) amino-C₁₋₆-alkyl,
- 10 c) amino-C₁₋₆-alkylamino,
- d) C₁₋₆-alkylamino-C₁₋₆-alkylamino,
- e) C₁₋₆-alkylamino-C₁₋₆-alkyl,
- f) arylamino-C₁₋₆-alkyl,
- g) aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl,
- 15 h) 4-10-membered heterocyclyl-C₁₋₆-alkylamino-C₁₋₆-alkyl,
- i) aryl,
- j) C₁₋₆-alkyl,
- k) optionally substituted aryl-C₁₋₆-alkyl,
- 20 l) heterocyclyl-C₁₋₆-alkyl,
- m) C₃₋₆-cycloalkyl-(CH₂)_n-,
- n) -OR⁹
- o) amino-C₁₋₆-alkoxy,
- p) N-(4-10-membered heterocyclyl-C₁₋₆-alkyl)amino,
- q) aryl-C₁₋₆-alkyl where the alkyl portion is substituted 25 with amino, hydroxy or C₁₋₆-alkylamino, and
- r) 4-10-membered heterocyclyl-C₁₋₆-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or C₁₋₆-alkylamino;

wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo; and the alkyl groups are optionally substituted with 1 to 3 groups selected from R⁵;

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wherein R^{8a} is selected from

- a) 5-10-membered heterocyclyl,
- b) aryl, and
- c) benzyl;

5 wherein the aryl and heterocyclyl groups are optionally substituted with 1 to 3 radicals selected from C₁₋₆-alkyl, halo, hydroxyl, alkoxy, amino, alkylamino, cyano, -NHC(O)R⁷, -COR⁷, C₁₋₆-haloalkyl and C₁₋₆-haloalkoxy; wherein R⁹ is selected from H, C₁₋₆-alkyl, alkenyl, C₃₋₆-

10 cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, aryl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 5-6-membered heteroarylarnino-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 15 arylamino-C₁₋₆-alkyl, aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 5-6-membered heteroaryloxy-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryloxy-C₁₋₆-alkyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-alkyl, C₁₋₆-hydroxyalkyl and C₁₋₆-alkoxy-C₁₋₆-alkyl;

20 wherein R^a are independently selected from H and C₁₋₆-alkyl; wherein k is 1; wherein m is 0, 1 or 2; wherein n is 0, 1, 2 or 3; and 25 wherein p is 1 or 2; and a pharmaceutically-acceptable salt thereof.

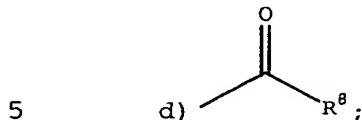
3. Compound of Claim 2 wherein Y is -NH-;

wherein R is phenyl ortho substituted with a radical 30 selected from R⁴ and optionally substituted with a radical selected from R⁴; wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are independently selected from R⁴; or wherein R^{1a} and R^{1b} or R^{1d} and R^{1c} form oxo;

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wherein R^2 is selected from

- a) - $(\text{CH}_2)_n$ -cycloalkyl,
 - b) - $(\text{CH}_2)_n$ -phenyl,
 - c) - $(\text{CH}_2)_n$ -5-10-membered heterocyclyl, and



wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 radicals selected from R⁴; and the heterocyclyl groups are, optionally substituted with 1 to 3 radicals selected from R⁴ and oxo;

10 wherein R³ is independently selected from H, chloro, bromo, iodo, phenyl, fluoro, amino, C₁₋₂-alkyl, C₁₋₂-haloalkyl, C₁₋₂-haloalkoxy, and C₁₋₂-alkoxy;

15 wherein R⁴ is selected from H, C₁₋₂-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl, -(CH₂)_n-phenyl, -(CH₂)_n-4-10-membered heterocyclyl, fluoro, chloro, -(CH₂)_n-OR^{9a}, -NR^{9a}SO₂R⁷, -NR^{9a}R^{9b}, -C(O)NR^{9a}R^{9b}, -NR^{9a}C(O)R⁷, cyano, nitro, -(CH₂)_n-C(O)R⁷, -C(O)OR^{9a}, -(CH₂)_n-C(S)R⁷, -(CH₂)_n-C=(NR^{9a})R⁷, -NR^{9a}C=(NR^{9a})N(R⁷)₂, -[C(R⁷)₂]pNR^{9a}R^{9b}, -[CH₂]_pNR^{9a}SO₂R⁷, -[CH₂]_pNR^{9a}C(O)R⁷, -SO₂NR^{9a}R^{9b}, -S(O)_mR⁷, -C(R⁷)₂SO₂CF₃, C₁₋₂-hydroxyalkyl C₁₋₂-haloalkyl and C₁₋₂-haloalkoxy;

20 wherein R⁵ is selected from halo, -OR^{9a}, -NR^{9a}R^{9b}, -[C(R⁷)₂]nNR^{9a}R^{9b}, and -SO₂NR^{9a}R^{9b};

25 wherein R⁶ is naphthyl or phenyl optionally substituted with one or two R³;

wherein R⁷ is selected from H, C₁₋₄-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl, -(CH₂)_n-phenyl, amino-C₁₋₄-alkyl, C₁₋₄-alkylamino, C₂₋₄-alkenyl, C₁₋₄-alkylthio-C₁₋₄-alkyl, C₁₋₄-alkylcarbonylamino-C₁₋₄-alkyl, C₁₋₄-alkylamino-C₁₋₄-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl and C₁₋₄-alkoxy;

30 wherein R⁸ is selected from

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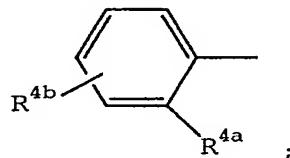
- a) amino-C₁₋₄-alkylamino,
- b) amino-C₁₋₄-alkyl,
- c) C₁₋₄-alkylamino-C₁₋₄-alkylamino,
- d) C₁₋₄-alkylamino-C₁₋₄-alkyl,
- 5 e) phenyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
- f) phenylamino-C₁₋₄-alkyl,
- g) 4-10-membered heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
- h) N-(4-10-membered heterocyclyl-C₁₋₄-alkyl)amino,
- i) C₁₋₄-alkyl,
- 10 j) C₃₋₆-cycloalkyl-(CH₂)_n-,
- k) aryl-(CH₂)_n-,
- l) 4-10-membered heterocyclyl-(CH₂)_n-,
- m) R^{9a}O-,
- n) amino-C₁₋₄-alkoxy,
- 15 o) phenyl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₄-alkylamino, and
- p) 4-10-membered heterocyclyl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or C₁₋₄-alkylamino;
- 20 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 3 groups selected from R⁴; and the heterocyclyl groups are optionally substituted with 1 to 3 groups selected from R⁴ and oxo;
- wherein R^{9a} is selected from H, C₁₋₆-alkyl, C₃₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, and phenyl-(CH₂)_n;
- 25 wherein R^{9b} is selected from H, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₃₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, phenyl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkylamino-C₁₋₆-alkyl, C₃₋₆-cycloalkyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 5-6-membered heteroaryl-amino-C₁₋₆-alkyl, 5-6-membered heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, phenylamino-C₁₋₆-alkyl, phenyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, 30 5-6-membered heteroaryloxy-C₁₋₆-alkyl, 5-6-membered

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heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, phenyl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, phenoxy-C₁₋₆-alkyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-alkyl, C₁₋₆-hydroxyalkyl and C₁₋₆-alkoxy-C₁₋₆-alkyl;

- 5 wherein R^a are independently H or methyl;
wherein k is 1;
wherein m is 0, 1 or 2;
wherein n is 0, 1, 2 or 3;
wherein p is 1 or 2; and
10 wherein q is 1;
- and a pharmaceutically-acceptable salt thereof.

4. Compound of Claim 3 wherein R is



- 15 wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are H;
wherein R² is selected from
 - a) -(CH₂)_n-C₃₋₆-cycloalkyl,
 - b) -(CH₂)_n-phenyl, and
 - c) -(CH₂)_n-6-10-membered heterocyclyl;
- 20 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 2 groups selected from R^{4b}; and
the heterocyclyl group is optionally substituted with
1 to 2 groups selected from R^{4b} and oxo;
- wherein R³ is independently selected from H, chloro, bromo,
25 iodo, fluoro, amino, methyl, trifluoromethyl,
trifluoromethoxy and methoxy;
- wherein R^{4a} is selected from -(CH₂)_n-OR^{9a}, -NR^{9a}SO₂R^{7a}, 4-6-membered heterocyclyl, -[CH₂]_pNR^{9a}SO₂R^{7a}, -NR^{9a}R^{9b}, -C(O)NR^{9a}R^{9b}, -NR^{9b}C(O)R^{7a}, -[CH₂]_pNR^{9b}C(O)R^{7a}, -(CH₂)_n-C(O)R^{7a},
30 nitro, -C(O)OR^{9a}, -(CH₂)_n-C(S)R^{7a}, -[C(R^{7a})₂]_pNR^{9a}R^{9b}, -SO₂NR^{9a}R^{9b}, -S(O)_mR^{7a} and -C(R^{7a})₂SO₂CF₃;

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wherein R^{4b} is selected from H, C₁₋₂-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl, -(CH₂)_n-phenyl, -(CH₂)_n-4-10-membered heterocyclyl, fluoro, chloro, -OR^{9a}, -(CH₂)_n-OR^{9a}, -NR^{9a}SO₂R^{7a}, -NR^{9a}R^{9b}, -C(O)NR^{9a}R^{9b}, -NR^{9a}C(O)R^{7b}, -(CH₂)_n-C(O)R^{7a}, nitro, -C(O)OR^{9a}, -(CH₂)_n-C(S)R^{7a}, -[C(R^{7a})₂]NR^{9a}R^{9b}, -SO₂NR^{9a}R^{9b}, -S(O)_mR^{7a}, -C(R^{7a})₂SO₂CF₃, cyano, C₁₋₂-haloalkyl and C₁₋₂-haloalkoxy;

5 wherein R^{7a} is selected from H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

10 wherein R^{7b} is selected from H, amino-C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkylamino, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

15 wherein R^{9a} is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, and phenyl-(CH₂)_n;

wherein R^{9b} is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, phenyl-(CH₂)_n-, amino-C₁₋₃-alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroarylarnino-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl, phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroaryloxy-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenoxy-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-hydroxyalkyl and C₁₋₃-alkoxy-C₁₋₃-alkyl;

20 wherein R^a are H;

wherein k is 1;

wherein m is 2;

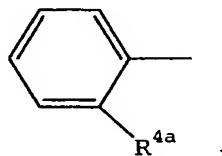
30 wherein n is 0, 1, 2 or 3; and

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wherein p is 1 or 2;

and a pharmaceutically-acceptable salt thereof.

5. Compound of Claim 4 wherein R is



5

wherein R² is selected from indolyl(CH₂)_n-, phenyl(CH₂)_n-, benzoxazolyl(CH₂)_n-, oxazolo[4,5-b]pyridyl(CH₂)_n-, oxazolo[5,4-b]pyridyl(CH₂)_n-, benzoxazolyl(CH₂)_n-, 1,2,3,4-tetrahydro-isoquinolyl(CH₂)_n-, pyridyl(CH₂)_n- and 10 2,3-dihydro-benzo[1,4]dioxanyl(CH₂)_n-;

wherein R² is optionally substituted with 1 to 2 groups selected from R^{4b};

wherein R³ is independently selected from H, chloro, bromo, amino, methyl, trifluoromethyl and methoxy;

15 wherein R^{4a} is selected from 4-5-membered heterocyclyl, -NR^{9a}SO₂R^{7a}, -NR^{9a}R^{9b}, -C(O)NR^{9a}R^{9b}, -C₁₋₃-NR^{9a}SO₂R^{7a}, -C₁₋₃-NR^{9a}C(O)R^{7b}, -NR^{9b}C(O)R^{7a} and -C₁₋₃-NR^{9a}R^{9b};

wherein R⁶ is phenyl optionally substituted with one or two R³;

20 wherein R^{7a} is selected from H, C₁₋₃-alkyl, -(CH₂)_n- C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

wherein R^{7b} is selected from H, amino-C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkylamino, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

25 wherein R^{9a} is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, and phenyl-(CH₂)_n-;

30

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wherein R^{9b} is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, phenyl-(CH₂)_n-, amino-C₁₋₃-alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroaryl-amino-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl, phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroaryloxy-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenyloxy-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-hydroxyalkyl and C₁₋₃-alkoxy-C₁₋₃-alkyl;

5 wherein k is 1;

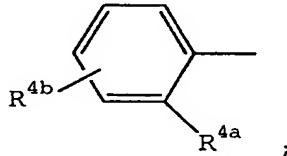
wherein m is 2;

10 wherein n is 0, 1, 2 or 3; and

wherein p is 1 or 2;

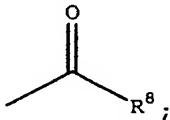
15 and a pharmaceutically-acceptable salt thereof.

6. Compound of Claim 3 wherein R is



20

wherein R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{1e}, and R^{1f} are H;
wherein R² is selected from



wherein R³ is independently selected from H, chloro, bromo, iodo, fluoro, amino, methyl, trifluoromethyl, trifluoromethoxy and methoxy;

25

wherein R^{4a} is selected from -C₁₋₂-alkyl-NR^{9a}SO₂R^{7a}, -NR^{9a}SO₂R^{7a}, 4-5-membered heterocyclyl-NR^{9a}R^{9b}, -C(O)NR^{9a}R^{9b}, -C₁₋₂-alkyl-NR^{9a}C(O)R^{7b}, -NR^{9b}C(O)R^{7a} and -C₁₋₂-alkyl-NR^{9a}R^{9b};

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wherein R^{4b} is selected from H, C₁₋₂-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl, -(CH₂)_n-phenyl, -(CH₂)_n-4-10-membered heterocyclyl, fluoro, chloro, -OR⁷, -NR⁷SO₂R⁷, -N(R⁷)₂, cyano, -(CH₂)_n-C(O)R⁷, -C(O)OR⁷, -(CH₂)_n-C(S)R⁷, -[C(R⁷)₂]pN(R⁷)₂, -SO₂N(R⁷)₂, -S(O)_mR⁷, -C(R⁷)₂SO₂CF₃, C₁₋₂-haloalkyl and C₁₋₂-haloalkoxy;

5 wherein R⁵ is selected from chloro, fluoro, hydroxyl, -NR^{7a}R^{7b} and -SO₂N(R^{7a})₂;

wherein R⁶ is phenyl optionally substituted with one or two

10 R³;

wherein R^{7a} is selected from H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

wherein R^{7b} is selected from H, amino-C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkylamino, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, -(CH₂)_n-4-10-membered heterocyclyl and -(CH₂)_n-phenyl;

15 wherein R⁸ is selected from

20 a) amino-C₁₋₄-alkylamino,

b) amino-C₁₋₄-alkyl,

c) C₁₋₄-alkylamino-C₁₋₄-alkylamino,

d) C₁₋₄-alkylamino-C₁₋₄-alkyl,

e) phenylamino-C₁₋₄-alkyl,

f) phenyl-C₁₋₂-alkylamino-C₁₋₄-alkyl,

25 g) 4-10-membered heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,

h) N-(4-10-membered heterocyclyl-C₁₋₄-alkyl)amino,

i) C₁₋₄-alkyl,

j) C₃₋₆-cycloalkyl-(CH₂)_n-,

30 k) aryl-(CH₂)_n-,

l) 4-10-membered heterocyclyl-(CH₂)_n-,

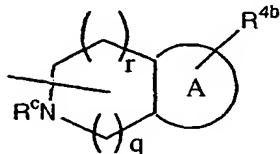
m) amino-C₁₋₄-alkoxy,

n) phenyl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₄-alkylamino, and

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o) 4-10-membered heterocyclyl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino;
 wherein the cycloalkyl and aryl groups are optionally substituted with 1 to 2 groups selected from R^{4b}; and the heterocyclyl groups are optionally substituted with 1 to 2 groups selected from R^{4b} and oxo;
 wherein R^{9a} is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, and phenyl-(CH₂)_n;;
 10 wherein R^{9b} is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n-, phenyl-(CH₂)_n-, amino-C₁₋₃-alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkylamino-C₁₋₃-alkyl, C₅₋₆-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroarylarnino-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl, phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6-membered heteroaryloxy-C₁₋₃-alkyl, 5-6-membered heteroaryl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkyloxy-C₁₋₃-alkyl, phenyloxy-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-hydroxyalkyl and C₁₋₃-alkoxy-C₁₋₃-alkyl;
 15 wherein R^a are H;
 wherein k is 1;
 20 wherein m is 2;
 wherein n is 0, 1, 2 or 3; and
 wherein p is 1 or 2;
 and a pharmaceutically-acceptable salt thereof.

30 7. Compound of Claim 6 wherein R⁸ is

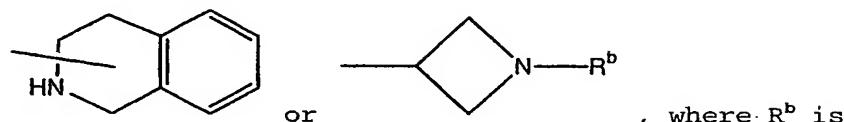


or optionally substituted azetidinyl;

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wherein A is selected from phenyl or 5-6-membered heteroaryl; wherein R^c is H or methyl; r is 0 or 1; and q is 0 or 1.

5 8. Compound of Claim 7 wherein R^b is



, where R^b is selected from H, C₁₋₆-alkyl, C₅₋₆-cycloalkyl-(CH₂)_n-, 4-10-membered heterocyclyl-(CH₂)_n- and phenyl-(CH₂)_n.

10

9. Compound of Claim 1 and pharmaceutically acceptable salts thereof selected from

((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-N-((1R)-2-[4-(2-methoxyphenyl)-piperidyl]-2-oxo-1-benzylethyl)carboxamide;

N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))carboxamide

N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((2S)-1-methylpyrrolidin-2-yl)carboxamide

N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((3S,1R)-3-aminocyclopentyl)carboxamide;

N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]((1S,3R)-3-aminocyclopentyl)carboxamide;

30 N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl](5-oxopyrrolidin-2-yl)carboxamide;

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N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]azetidin-3-ylcarboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
5 [(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]-
2-(4-piperidyl)acetamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((2S,3R)-3-phenylpyrrolidin-2-yl)carboxamide;
10 N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((2S)pyrrolidin-2-yl)carboxamide;
((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-N-[(1R)-1-[(3,4-
dichlorophenyl)methyl]-2-(4-{2-[
15 [(methylsulfonyl)amino]phenyl}piperidyl)-2-
oxoethyl]carboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
[(cyclopropylmethyl)-
[(methylsulfonyl)amino]phenyl}piperidyl)-2-
20 oxoethyl]((3S)(3-1,2,3,4-
tetrahydroisoquinolyl))carboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
[(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-
piperidyl)-2-oxoethyl]azetidin-3-ylcarboxamide;
25 N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-
(trifluoromethyl)phenyl]-piperidyl}ethyl)((3S)(3-
1,2,3,4-tetrahydroisoquinolyl))carboxamide;
N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-
30 (hydroxyethyl)phenyl]piperidyl}-2-oxoethyl)((3S)(3-
1,2,3,4-tetrahydroisoquinolyl))carboxamide;
N-[(1R)-2-(4-{2-[(2-aminoethyl)(methylsulfonyl)amino]-
phenyl)piperidyl)-1-[(4-chlorophenyl)methyl]-2-
oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-
carboxamide;

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((3S) (3-1,2,3,4-tetrahydroisoquinolyl))-N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(3-methyl-2-oxo(4-imidazolinyl)phenyl]piperidyl}-2-oxoethyl)carboxamide;

5 ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))-N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl]piperidyl}ethyl)carboxamide;

N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl]-piperidyl}ethyl)azetidin-3-

10 ylcarboxamide;

tert-butyl 3-(N-((1R)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl) (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;

N-((1R)-1-[(4-chlorophenyl)methyl]-2-[4-(2-((2-cyanophenyl)sulfonyl)amino)-phenyl)piperidyl]-2-

15 oxoethyl}((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;

N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-[4-(2-((2,4,6-trimethylphenyl)sulfonyl)amino)phenyl)piperidyl]ethyl}

20 ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;

N-((1R)-1-[(4-chlorophenyl)methyl]-2-(4-((2-(methylamino)carbonylamino)-phenyl)piperidyl)-2-

oxoethyl}((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;

25 N-((1R)-1-[(4-chlorophenyl)methyl]-2-{4-[2-(methoxycarbonylamino)phenyl]piperidyl}-2-

oxoethyl}((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;

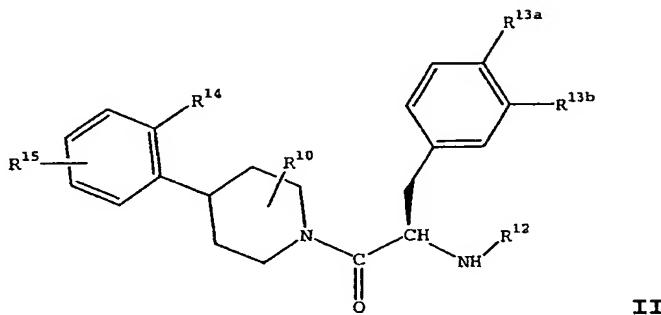
N-((1R)-1-[(4-chlorophenyl)methyl]-2-(4-((2-(cyclopropylmethyl)amino)-phenyl)piperidyl)-2-

30 oxoethyl}((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide; and

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N-[(1R)-2-(4-{2-[(2-aminoethyl)amino]phenyl}piperidyl)-1-[(4-chlorophenyl)methyl]-2-oxoethyl][(3S)(3-1,2,3,4-tetrahydroisoquinolyl)]carboxamide.

5 10. A compound of formula II



wherein R¹⁰ is selected from H, chloro or fluoro; or wherein
10 R¹⁰ is a C₁₋₄-alkylene bridge;
wherein R¹² is selected from optionally substituted phenyl-C₁₋₂-alkylenyl, optionally substituted 5-10 membered

heteroaryl and heterocyclyl; provided the optionally substituted heterocyclyl is not nitro substituted;

15 wherein R^{13a} and R^{13b} are independently selected from H, fluoro, iodo, bromo, chloro, C₁₋₂-alkyl, C₁₋₂-haloalkyl, phenyl, and C₁₋₂-alkoxy; or wherein R^{13a} and R^{13b} together form an C₁₋₄-alkylenyl bridge;
wherein R¹⁴ is selected from R¹⁹R²⁰N-, R¹⁹R²⁰N-C₁₋₄-alkyl,
20 (R²¹R²²N-)(O=C)-, C₁₋₄-haloalkyl, C₂₋₄-hydroxyalkyl, heterocycloloxy-C₁₋₄-alkyl, aryloxy-C₁₋₄-alkyl and C₁₋₄-alkoxycarbonyl;

wherein R¹⁵ is selected from H, C₁₋₂-haloalkyl, C₁₋₄-alkyl, halo, -OR¹⁷, and -N(R¹⁷)₂;
25 wherein R¹⁶ is selected from

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- a) 4-6 membered saturated heterocyclyl,
- b) 10 membered partially unsaturated heterocyclyl,
- c) 5-10 membered heteroaryl,
- d) C₁₋₄-aminoalkyl,
- 5 e) C₁₋₄-aminoalkylamino,
- f) C₁₋₄-alkylamino-C₁₋₄-alkylamino,
- g) C₁₋₄-alkylamino-C₁₋₄-alkyl,
- h) arylamino-C₁₋₄-alkyl,
- i) aryl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
- 10 j) heterocyclyl-C₁₋₄-alkylamino-C₁₋₄-alkyl,
- k) aryl, provided if 2-substituted aryl, is 2-substituted with amino or chloro,
- l) C₁₋₄-alkyl,
- m) aralkyl,
- 15 n) heterocyclyl-C₁₋₄-alkyl, provided R¹⁶ is not 3-methylindol-1-ylethyl,
- o) C₅₋₆-cycloalkyl,
- p) C₁₋₄-aminoalkoxy,
- q) heterocyclyl-C₁₋₄-alkoxy,
- 20 r) N-(heterocyclyl-C₁₋₄-alkyl)amino,
- s) aryl-C₁₋₄-alkyl where the alkyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino, and
- t) heterocyclyl-C₁₋₄-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or -C₁₋₄-alkylamino;
- 25 wherein R¹⁷ is selected from H, C₁₋₄-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, and aryl-(CH₂)_n-;
- wherein R¹⁹ is selected from H, R²³SO₂-, C₁₋₆-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, amino-C₁₋₆-alkyl, C₁₋₆-alkylamino-C₁₋₆-alkyl, C₃₋₇-cycloalkylamino-C₁₋₆-alkyl, C₃₋₇-cycloalkyl-C₁₋₆-alkylamino-C₁₋₆-alkyl, heteroaryl-amino-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, arylamino-C₁₋₆-alkyl, aryl-C₁₋₆-alkylamino-C₁₋₆-alkyl, heteroaryloxy-C₁₋₆-alkyl, heteroaryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, aryloxy-C₁₋₆-alkyl, aryl-C₁₋₆-alkyloxy-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkyl, C₁₋₆-

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- alkylthio-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkylcarbonyl, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxy-C₁₋₆-alkylcarbonyl, C₁₋₆-alkylaminocarbonyl, arylcarbonyl, aralkylcarbonyl, C₃₋₇-cycloalkylcarbonyl, C₃₋₇-cycloalkyl-C₁₋₆-alkylcarbonyl, heteroaryl-C₁₋₆-alkylcarbonyl and heteroarylcarbonyl;
- 5 wherein R²⁰ is selected from H, C₁₋₈-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, C₁₋₃-alkylsulfonyl, amino-C₁₋₃-alkyl, heterocyclyl-(CH₂)_n-, and aryl-(CH₂)_n;
- 10 alternatively R¹⁹ and R²⁰ together with the nitrogen atom form a 4-8 membered heterocyclic ring;
- wherein R²¹ is selected from H, C₁₋₆-alkyl, C₂₋₆-alkenyl, C₁₋₆-alkylthio-C₁₋₆-alkyl, C₁₋₆-alkylcarbonylamino-C₁₋₆-alkyl, amino-C₁₋₆-alkyl, heterocyclyl-(CH₂)_n-, C₃₋₇-cycloalkyl-(CH₂)_n-, and aryl-(CH₂)_n;
- 15 wherein R²² is selected from H, C₁₋₆-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, heterocyclyl-(CH₂)_n- and aryl-(CH₂)_n;
- alternatively R²¹ and R²² together with the amide nitrogen atom form a 4-7 membered saturated heterocyclic ring;
- 20 wherein R²³ is selected from H, C₁₋₆-alkyl, C₃₋₇-cycloalkyl-(CH₂)_n-, heterocyclyl-(CH₂)_n- and aryl-(CH₂)_n;
- wherein n is 0, 1, 2 or 3; and
- wherein m is 0, 1 or 2;
- wherein aryl, heterocyclyl and cycloalkyl are optionally substituted with one or more substituents selected from C₁₋₂-haloalkyl, C₁₋₃-alkyl, C₃₋₆-cycloalkyl-(CH₂)_n-, chloro, fluoro, -OR¹⁷, -NR¹⁷SO₂R¹⁷, N(R¹⁷)₂, cyano, -COR¹⁷, -C(R¹⁷)₂N(R¹⁷)₂, nitro, -SO₂N(R¹⁷)₂, -S(O)_mR¹⁷, and C₁₋₃-haloalkoxy;
- 25 and a pharmaceutically-acceptable salt thereof.

11. Compound of Claim 10 wherein R¹⁰ is H;
wherein R^{13a} is selected from H, bromo, chloro, phenyl, trifluoromethyl and methoxy;

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wherein R^{13b} is H;

wherein R¹⁵ is selected from H and C₁₋₂-haloalkyl

wherein R¹⁶ is selected from

- a) 4-6 membered saturated heterocyclyl,
 - 5 b) 10 membered partially unsaturated heterocyclyl,
 - c) 5-10 membered heteroaryl,
 - d) C₁₋₃-aminoalkyl,
 - e) C₁₋₃-aminoalkylamino,
 - f) C₁₋₃-alkylamino-C₁₋₃-alkylamino,
 - 10 g) C₁₋₃-alkylamino-C₁₋₃-alkyl,
 - h) phenylamino-C₁₋₃-alkyl,
 - i) phenyl-C₁₋₄-alkylamino-C₁₋₃-alkyl,
 - j) heterocyclyl-C₁₋₃-alkylamino-C₁₋₃-alkyl,
 - 15 k) phenyl, naphthyl or tetrahydronaphthyl, provided R¹⁶ is not 2-methoxyphenyl, 2-phenoxyphenyl or 2-phenylaminophenyl,
 - l) C₁₋₃-alkyl,
 - m) phenyl-C₁₋₂-alkyl,
 - n) 5-10-membered saturated or partially unsaturated heterocyclymethyl,
 - 20 o) 5-6 membered heteroaryl-C₁₋₄-alkyl,
 - p) optionally substituted C₅₋₆-cycloalkyl,
 - q) C₁₋₃-aminoalkoxy,
 - r) [5- or 6- membered heterocyclyl]-C₁₋₃-alkoxy,
 - 25 s) N-(5-10-membered heterocyclyl-C₁₋₃-alkyl)amino,
 - t) phenyl-C₁₋₂-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino, and
 - u) 5- or 6- membered heterocyclyl-C₁₋₃-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy
 - 30 or C₁₋₃-alkylamino;
- wherein R¹⁷ is selected from H, C₁₋₃-alkyl, -(CH₂)_n-C₃₋₆-cycloalkyl, and -(CH₂)_n-phenyl;
- wherein R¹⁹ is selected from H, R²³SO₂-, C₁₋₆-alkyl, amino-C₁₋₃-alkyl, C₁₋₆-alkylamino-C₁₋₃-alkyl, C₃₋₅-cycloalkylamino-C₁₋₃-

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alkyl, C₃₋₅-cycloalkyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkoxy-C₁₋₃-alkyl,
heteroaryl amino-C₁₋₃-alkyl, 5-6 membered heteroaryl-C₁₋₃-alkylamino-C₁₋₃-alkyl, phenylamino-C₁₋₃-alkyl, phenyl-C₁₋₃-alkylamino-C₁₋₃-alkyl, 5-6 membered heteroaryloxy-C₁₋₃-alkyl, phenoxy-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxy-C₁₋₃-alkyl, C₁₋₆-alkylcarbonyl, C₁₋₃-alkoxycarbonyl, C₁₋₃-alkoxy-C₁₋₃-alkylcarbonyl, C₁₋₃-alkylaminocarbonyl, C₃₋₆-cycloalkylcarbonyl, C₃₋₆-cycloalkyl-C₁₋₃-alkylcarbonyl,
phenylcarbonyl, phenyl-C₁₋₃-alkylcarbonyl, 5- or 6-membered heteroaryl-C₁₋₃-alkylcarbonyl, 5- or 6- membered heteroarylcarbonyl and -(CH₂)_n-C₃₋₅-cycloalkyl optionally substituted with C₁₋₂-alkoxycarbonyl;
wherein R²⁰ is selected from H, C₁₋₇-alkyl, -(CH₂)_n-C₅₋₆-cycloalkyl, -(CH₂)_n-5-6-membered heterocyclyl, C₁₋₃-alkylsulfonyl, amino-C₁₋₃-alkyl and -(CH₂)_n-phenyl;
alternatively R¹⁹ and R²⁰ together with the nitrogen atom form a 4-7 membered heterocyclic ring;
wherein R²¹ is selected from H, C₁₋₃-alkyl, C₂₋₃-alkenyl, C₁₋₃-alkylthio-C₁₋₃-alkyl, C₁₋₃-alkylcarbonylamino-C₁₋₃-alkyl, amino-C₁₋₃-alkyl, -(CH₂)_n-[5- or 6- membered heterocyclyl], -(CH₂)_n-C₅₋₆-cycloalkyl, and -(CH₂)_n-phenyl;
wherein R²² is selected from H, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, -(CH₂)_n-[5- or 6- membered heterocyclyl] and -(CH₂)_n-phenyl;
alternatively R²¹ and R²² together with the amide nitrogen atom form a 5-6 membered heterocyclic ring; and
wherein R²³ is selected from H, C₁₋₃-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, -(CH₂)_n-[5- or 6- membered heterocyclyl] and -(CH₂)_n-phenyl;
wherein phenyl, cycloalkyl and heterocyclyl are optionally substituted with one or more substituents selected from C₁₋₂-haloalkyl, C₁₋₂-alkyl, -(CH₂)_n-C₄₋₆-cycloalkyl, chloro, fluoro, -OR¹⁷, -NR¹⁷SO₂R¹⁷, N(R¹⁷)₂, cyano, -COR¹⁷, -

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$C(R^{17})_2N(R^{17})_2$, nitro, $-SO_2N(R^{17})_2$, $-S(O)_mR^{17}$, and $C_{1-2}-$ haloalkoxy;

and pharmaceutically-acceptable salts thereof.

- 5 12. Compound of Claim 11 wherein R^{13a} is selected from H, bromo, phenyl and chloro;
- wherein R^{14} is selected from trifluoromethyl, 2-hydroxyethyl, 1-hydroxyethyl, $R^{19}R^{20}N-$, $R^{19}R^{20}N-C_{1-2}-$ alkyl and $(R^{21}R^{22}N-)(O=)C-$;
- 10 wherein R^{15} is H or trifluoromethyl;
- wherein R^{17} is selected from H, methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenylpropyl, phenylethyl, benzyl and phenyl;
- 15 wherein R^{19} is selected from H, $R^{23}SO_2-$, methyl, ethyl, propyl, isopropyl, isopentyl, 3-ethylbutyl, hydroxymethyl, hydroxyethyl, cyclopropylmethyl, 1-(ethoxycarbonyl)cycloprop-2-ylmethyl, $R^{23}SO_2-$, aminomethyl, aminoethyl, dimethylaminoethyl,
- 20 diethylaminoethyl, dipropylaminoethyl, di-isobutylaminoethyl, di-(*tert*-butylmethyl)aminoethyl, di-(3-ethylbutyl)aminoethyl, di-(cyclohexylmethyl)aminoethyl, furylmethylaminoethyl, thienylmethylaminoethyl, benzylaminoethyl,
- 25 di(furylmethyl)aminoethyl, di(cyclopropylmethyl)aminoethyl, di(thienylmethyl)aminoethyl, di(benzyl)aminoethyl, phenylmethoxyethyl, pyridyloxymethyl, methylthiopropyl, methylcarbonyl, ethylcarbonyl, propylcarbonyl,
- 30 isopropylcarbonyl, isobutylcarbonyl, butylcarbonyl, *tert*-butylcarbonyl, pentylcarbonyl, cyclopentylcarbonyl, cyclopropylcarbonyl, cyclobutylcarbonyl, cyclohexylcarbonyl, methoxycarbonyl, methoxymethylcarbonyl, ethoxycarbonyl, propoxycarbonyl,

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methylaminocarbonyl, ethylaminocarbonyl,
propylaminocarbonyl, optionally substituted
thienylmethylcarbonyl, optionally substituted
benzylcarbonyl, optionally substituted
5 phenylethylcarbonyl, optionally substituted
phenylcarbonyl and optionally substituted
pyridylcarbonyl;
wherein R²⁰ is selected from H, methyl, ethyl, propyl,
isopropyl, butyl, isobutyl, pentyl, hexyl, heptyl,
10 cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,
cyclohexylmethyl, cyclopropyl, cyclohexyl,
methylsulfonyl, aminoethyl, optionally substituted
phenyl, optionally substituted imidazolyl, optionally
substituted imidazolylmethyl, optionally substituted
15 thienylmethyl, optionally substituted furylmethyl,
optionally substituted pyrrolidinylmethyl, optionally
substituted pyridylmethyl, optionally substituted
thienylmethyl, optionally substituted benzyl, optionally
substituted phenylethyl and optionally substituted
20 phenylpropyl;
alternatively R¹⁹ and R²⁰ together with the nitrogen atom
form a heterocyclic ring selected from triazolyl,
tetrazolyl, 2-pyridone, oxo-pyrrolidinyl, 2-oxo-
piperidinyl, 4,5-dihydro-2-oxo-oxazolyl, 1,1-dioxo-
25 isothiazolidin-2-yl, 2-oxo-imidazolin-1-yl, 3-methyl-2-
oxo-imidazolin-1-yl, piperidinyl optionally
substituted with one or more substituents selected
from methyl, ethyl, propyl, and isopropyl,
piperazinyl optionally substituted with one or more
30 substituents selected from methyl, ethyl, propyl, and
isopropyl,
imidazolyl optionally substituted with one or more
substituents selected from methyl, ethyl, propyl, and
isopropyl, and

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- pyrrolidinyl optionally substituted with one or more substituents selected from methyl, ethyl, propyl, and isopropyl;
- wherein R²¹ is selected from H, methyl, ethyl, propyl,
5 isopropyl, allyl, methylthioethyl, methylthiomethyl, methylcarbonylaminoethyl, methylcarbonylaminomethyl, aminomethyl, aminoethyl, 1-methylpyrrolidinylethyl, piperidinylethyl, pyridyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, 4-chlorophenylmethyl, 4-
10 phenoxyphenylethyl, benzyl and phenylethyl;
wherein R²² is H or methyl;
alternatively R²¹ and R²² together form a ring selected from pyrrolidinyl, morpholino, piperidinyl, piperazinyl, 4-acetyl piperazinyl and 4-methyl piperazinyl; and
15 wherein R²³ is selected from H, methyl, ethyl, propyl, optionally substituted thiienyl, optionally substituted phenyl, optionally substituted benzyl, optionally substituted phenylethyl and optionally substituted phenylpropyl;
20 wherein phenyl, cycloalkyl and heterocyclyl are optionally substituted with one or more substituents selected from trifluoromethyl, methyl, nitro, cyano, chloro, methoxy, phenoxy, acetyl, amino, dimethylamino and aminomethyl; and pharmaceutically-acceptable salts thereof.
25
13. Compound of Claim 12 wherein R¹⁴ is selected from N-pyrrolidinyl carbonyl, N-morpholinocarbonyl, N-piperidinylethylaminocarbonyl, benzylaminocarbonyl, N-methyl-N-benzylaminocarbonyl, aminoethylaminocarbonyl, 30 pyridylaminocarbonyl, methylthioethylaminocarbonyl, methylcarbonylaminoethylaminocarbonyl, 1-methylpyrrolidinylethylaminocarbonyl, phenethylaminocarbonyl, phenylaminocarbonyl, cyclohexylmethylaminocarbonyl, N-methyl-N-

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phenethylaminocarbonyl, N,N-dimethylaminocarbonyl, 4-chlorophenylmethylaminocarbonyl,
phenoxyphenethylaminocarbonyl, allylaminocarbonyl, 4-methylpiperazinylcarbonyl, 4-acetylpiperazinylcarbonyl,
5 isopropylaminocarbonyl,
1-(N-cyclopropylmethylamino)ethyl, 1-(N-methyl-N-methylcarbonylamino)ethyl, 1-(N-isopropylamino)ethyl, 1-(N-isobutyl-N-methylamino)ethyl, N-cyclopropylmethyl-N-propylaminomethyl, N,N-dicyclopropylmethylaminomethyl, 1-(N-
10 propyl-N-methylamino)ethyl, 1-(N-methyl-N-methylsulfonylamino)ethyl, triazolylmethyl, imidazol-1-ylmethyl, 2-isopropylimidazol-1-yl-methyl, 2-propylimidazol-1-yl-methyl, 2-oxo-pyrid-1-yl-methyl, 3-pyridyl-oxymethyl,
2-methylimidazol-1-yl-methyl, tetrazolylmethyl, 2,5-
15 dimethylpyrrolidin-1-ylmethyl, 2-oxo-pyrrolidin-1-yl-methyl, 2-oxo-piperidin-1-yl-methyl, 4,5-dihydro-2-oxo-oxazol-3-yl-methyl, pyrrolidin-1-ylmethyl, 2,6-dimethylpiperidin-1-ylmethyl, piperazin-1-yl-methyl, 4-methylpiperazin-1-yl-methyl, piperidin-1-yl-methyl, 1-(N-ethyl-N-
20 methylamino)ethyl, 1-(N,N-dipropylamino)ethyl, 1-(N,N-diisopropylamino)ethyl, 1-(N-(1-ethoxycarbonyl)cycloprop-2-ylmethyl-N-methylamino)ethyl, 1-(N-(2-methylbutyl)-N-methylamino)ethyl, 1-(N-(4-methylcarbonylaminophenyl)methyl-N-methylamino)ethyl, 1-(N-methylamino)ethyl, 1-(N,N-
25 dimethylamino)ethyl, N,N-dimethylaminomethyl, N-cyclopropylmethyl-N-methylsulfonylaminoethyl, 1-(N-(3-thienyl)methyl-N-methylamino)ethyl, 1-(N-phenylmethoxyethyl-N-methylamino)ethyl, 1-(N-(2-methoxyphenyl)methyl-N-methylamino)ethyl, 1-(N-(4-pyridyl)methyl-N-
30 methylamino)ethyl, 1-(N-(2-pyrrolidinyl)methyl-N-methylamino)ethyl, 1-(N-(3-methoxyphenyl)methyl-N-methylamino)ethyl, 1-(N-(4-methoxyphenyl)methyl-N-methylamino)ethyl, 1-(N-benzyl-N-methylamino)ethyl, 1-(N-methyl-N-aminoethylamino)ethyl, 1-(N-cyclohexylmethyl-N-

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- methylamino)ethyl, N,N-dimethylaminomethyl, N-(1-hydroxyethyl)-N-methylaminomethyl, N-(1-hydroxyethyl)-N-methylaminomethyl,
- N-propyl-N-methylsulfonylamino, N-(methylsulfonyl)-N-propylamino, N-(methylsulfonyl)-N-cyclopropylmethy lamino, N-(methylsulfonyl)-N-aminoethylamino, N-(methylsulfonyl)-N-(N',N'-dimethylaminoethyl)amino, N-(N',N'-diethylaminoethyl)-N-methylsulfonylamino, N-(N',N'-dipropylaminoethyl)-N-methylsulfonylamino, N-(N',N'-diisobutylaminoethyl)-N-methylsulfonylamino, N-(N',N'-di-tert-butylmethylaminoethyl)-N-methylsulfonylamino, N-(N',N'-di(3-ethylbutyl)aminoethyl)-N-methylsulfonylamino, N-(N',N'-di(cyclopropylmethyl)aminoethyl)-N-methylsulfonylamino, N-(N',N'-di(cyclohexylmethyl)aminoethyl)-N-methylsulfonylamino, N-(N',N'-di(2-furylmethyl)aminoethyl)-N-methylsulfonylamino, N-(N',N'-di(3-thienylmethyl)aminoethyl)-N-methylsulfonylamino, N-(N',N'-di(benzyl)aminoethyl)-N-methylsulfonylamino, N-(methylsulfonyl)-N-isobutylamino, N-(methylsulfonyl)-N-methylamino, N-(methylsulfonyl)-N-phenethylamino, N-(methylsulfonyl)amino, N-(benzylsulfonyl)amino, N-(propylsulfonyl)amino, N-(phenylsulfonyl)amino, N-(methylsulfonyl)-N-phenylpropylamino, thienylsulfonylamino, (2-nitrophenyl)methylsulfonylamino, (2,4,6-trimethylphenyl)sulfonylamino, (2-cyanophenyl)sulfonylamino, N-methoxymethylcarbonyl-N-cyclopropylmethy lamino, N-methylcarbonyl-N-cyclopropylmethy lamino, N-phenylcarbonyl-N-cyclopropylmethy lamino, N-(3-methoxyphenylcarbonyl)-N-cyclopropylmethy lamino, N-benzylcarbonyl-N-cyclopropylmethy lamino, N-cyclopropylmethy lamino, N-cyclohexylcarbonyl-N-cyclopropylmethy lamino, N-thienylmethylcarbonyl-N-cyclopropylmethy lamino, N-phenylethyl-N-cyclopropylmethy lamino, N-(2-imidazolyl)-N-cyclopropylmethy lamino, N-(4-methyl-5-imidazolyl)-N-

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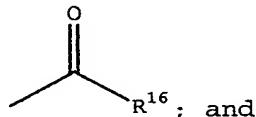
cyclopropylmethylamino, N-(4-methyl-5-imidazolylmethyl)-N-
cyclopropylmethylamino, N-(4-imidazolylmethyl)-N-
cyclopropylmethylamino, N-(5-imidazolylmethyl)-N-
cyclopropylmethylamino, N-(2-thienylmethyl)-N-
5 cyclopropylmethylamino, N-(3-thienylmethyl)-N-
cyclopropylmethylamino, N-(3-furylmethyl)-N-
cyclopropylmethylamino, N-(4-imidazolyl)-N-
cyclopropylmethylamino, N-cyclopentylcarbonyl-N-
cyclopropylmethylamino, N-cyclohexylcarbonyl-N-
10 cyclopropylmethylamino, N-methylthiopropyl-N-
cyclopropylmethylamino, N-ethylcarbonyl-N-
cyclopropylmethylamino, N-isopropylcarbonyl-N-
cyclopropylmethylamino, N-isobutylcarbonyl-N-
cyclopropylmethylamino, N-ethyl-N-cyclopropylmethylamino, N-
15 isobutyl-N-cyclopropylmethylamino, N-cyclopropylcarbonyl-N-
cyclopropylmethylamino, N,N-di(cyclopropylmethyl)amino,
N-methoxymethylcarbonyl-N-aminoethylamino, N-
ethylcarbonyl-N-aminoethylamino, N-isopropylcarbonyl-N-
aminoethylamino, N-isobutylcarbonyl-N-aminoethylamino, N-
20 tert-butylcarbonyl-N-aminoethylamino, N-propylcarbonyl-N-
aminoethylamino, N-pentylcarbonyl-N-aminoethylamino, N-
ethyl-N-aminoethylamino, N-propyl-N-aminoethylamino, N-
cyclopropyl-N-aminoethylamino, N-cyclopropylmethyl-N-
aminoethylamino, N-cyclobutylmethyl-N-aminoethylamino, N-
25 butyl-N-aminoethylamino, N-pentyl-N-aminoethylamino, N-
hexyl-N-aminoethylamino, N-heptyl-N-aminoethylamino, N-(3-
ethylbutyl)-N-aminoethylamino, N-cyclohexylcarbonyl-N-
aminoethylamino, N-phenylcarbonyl-N-aminoethylamino, N-(3-
methoxyphenyl)carbonyl-N-aminoethylamino, N-benzylcarbonyl-
30 N-aminoethylamino, N-phenylethylcarbonyl-N-aminoethylamino,
N-pyridylcarbonyl-N-aminoethylamino, N-thienylmethyl-N-
aminoethylamino,
aminoethylamino, pyridylcarbonylamino, N-
cyclopropylmethylamino, methylcarbonylamino,

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methoxycarbonylamino, trifluoromethyl, 2-hydroxyethyl, 1-hydroxyethyl, methylaminocarbonylamino, 1,1-dioxoisothiazolidin-2-yl, 2-oxo-imidazolin-1-yl and 3-methyl-2-oxo-imidazolin-1-yl;

5 and pharmaceutically-acceptable salts thereof.

14. Compound of Claim 12 wherein R¹² is selected from



10 wherein R¹⁶ is selected from

- a) 4-6 membered saturated heterocyclyl,
- b) 10 membered partially saturated heterocyclyl,
- c) 5-10 membered heteroaryl,
- d) C₁₋₃-aminoalkyl,
- 15 e) C₁₋₃-aminoalkylamino,
- f) C₁₋₃-alkylamino-C₁₋₃-alkylamino,
- g) C₁₋₃-alkylamino-C₁₋₃-alkyl,
- h) phenylamino-C₁₋₃-alkyl,
- i) phenyl-C₁₋₄-alkylamino-C₁₋₃-alkyl,
- 20 j) heterocyclyl-C₁₋₃-alkylamino-C₁₋₃-alkyl,
- k) phenyl, naphthyl or tetrahydronaphthyl,
- l) C₁₋₃-alkyl,
- m) phenyl-C₁₋₂-alkyl,
- n) 5-10-membered saturated or partially unsaturated
- 25 heterocyclylmethyl,
- o) 5-6 membered heteroaryl-C₁₋₄-alkyl,
- p) optionally substituted C₅₋₆-cycloalkyl,
- q) C₁₋₃-aminoalkoxy,
- r) [5- or 6- membered heterocyclyl]-C₁₋₃-alkoxy,
- 30 s) N-(5-10-membered heterocyclyl-C₁₋₃-alkyl)amino,
- t) phenyl-C₁₋₂-alkyl where the alkyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino, and

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u) 5- or 6- membered heterocyclyl-C₁₋₃-alkylenyl where the alkylenyl portion is substituted with amino, hydroxy or C₁₋₃-alkylamino;
wherein the heterocyclyl, aryl and cycloalkyl groups are
5 optionally substituted;
and pharmaceutically-acceptable salts thereof.

15. Compound of Claim 14 wherein R¹⁶ is selected from N-(piperidylmethyl)amino, aminopropylamino, aminomethyl,
10 aminoethyl, aminopropyl, N-methylaminomethyl, N-(4-chlorophenyl)aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl, 2-aminoethyl, aminoproxy, pyrrolidinylmethoxy, N-methylaminoethylamino, 3-aminocyclopentyl, 4-aminocyclohexyl, 1-aminocyclohexyl, 2-indolyl, octahydro-indolyl, 1-methylindol-2-yl, 3-pyridyl,
15 2-pyridyl, N-methylbenzopyrrolyl, 5-benzopyrrolyl, 2-benzofuran, benzodioxolyl, 2-benzothienyl, 4-imidazolylmethyl, 3-azetidinyl optionally
N-substituted with a substituent selected from methyl,
20 ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, cyclohexylmethyl and benzyl,
6-quinolyl, 2-quinolyl, 3-isouinolyl, tetrahydroisoquinolyl, N-methylpyrrolidin-2-yl, pyrrolidin-2-yl, 5-oxopyrrolidin-2-yl, 3-phenylpyrrolidin-2-yl, (1-methyl-5-oxo-2-(pyridin-3-yl)-pyrrolidin-3-yl)methyl,
25 thienyl, 4-piperidyl, 4-piperidylmethyl, N-methyl-4-piperidyl, N-methyl-2-piperidyl, N-ethyl-4-piperidyl, N-isobutyl-4-piperidyl, 3-piperidyl, 3-(aminomethyl)phenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 2-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 2-aminophenyl, 3-aminophenyl, isopropyl, 4-chlorophenylmethyl, benzyl, phenyl-2-hydroxyethyl, 1-(amino)benzyl, 2-(1,2,3,4-

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tetrahydronaphthyl), naphthyl, (2-benzylamino)ethyl,
imidazol-4-yl-(1-amino)ethyl, phenyl-1-(methylamino)ethyl
and phenyl-1-(amino)ethyl;
and pharmaceutically-acceptable salts thereof.

5

16. Compound of Claim 15 and pharmaceutically
acceptable salts thereof selected from

- N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
10 [(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((3S)(3-1,2,3,4-
tetrahydroisoquinolyl))carboxamide
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
15 oxoethyl]((2S)-1-methylpyrrolidin-2-yl)carboxamide
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((3S,1R)-3-aminocyclopentyl)carboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
20 [(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((1S,3R)-3-aminocyclopentyl)carboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl](5-oxopyrrolidin-2-yl)carboxamide;
25 N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]azetidin-3-ylcarboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-oxoethyl]-
30 2-(4-piperidyl)acetamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((2S,3R)-3-phenylpyrrolidin-2-yl)carboxamide;

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N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
[(methylsulfonyl)amino]phenyl}-piperidyl)-2-
oxoethyl]((2S)pyrrolidin-2-yl)carboxamide;
((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-N-[(1R)-1-[(3,4-
5 dichlorophenyl)methyl]-2-(4-{2-[
[(methylsulfonyl)amino]phenyl}piperidyl)-2-
oxoethyl]carboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
10 [(cyclopropylmethyl)-
[(methylsulfonyl)amino]phenyl}piperidyl)-2-
oxoethyl]((3S)(3-1,2,3,4-
tetrahydroisoquinolyl))carboxamide;
N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-{2-[
15 [(cyclopropylmethyl)-(methylsulfonyl)amino]phenyl}-
piperidyl)-2-oxoethyl]azetidin-3-ylcarboxamide;
N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-(4-[2-
1,2,3,4-tetrahydroisoquinolyl])carboxamide;
N-((1R)-1-[(4-chlorophenyl)methyl]-2-(4-[2-
20 (hydroxyethyl)phenyl)piperidyl)-2-oxoethyl)((3S)(3-
1,2,3,4-tetrahydroisoquinolyl))carboxamide;
N-[(1R)-2-(4-{2-[(2-aminoethyl)(methylsulfonyl)amino]-
25 phenyl}piperidyl)-1-[(4-chlorophenyl)methyl]-2-
oxoethyl]((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-
carboxamide;
((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-N-((1R)-1-[(4-
chlorophenyl)methyl]-2-(4-[2-(3-methyl-2-oxo(4-
imidazolinyl)phenyl)piperidyl)-2-
oxoethyl]carboxamide;
30 ((3S)(3-1,2,3,4-tetrahydroisoquinolyl))-N-((1R)-1-[(4-
chlorophenyl)methyl]-2-oxo-2-(4-[2-(2-oxo(4-
imidazolinyl)phenyl)piperidyl]ethyl)carboxamide;

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- N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-{4-[2-(2-oxo(4-imidazolinyl)phenyl)-piperidyl]ethyl}azetidin-3-ylcarboxamide;
- 5 tert-butyl 3-(N-((1R)-2-[4-(2-aminophenyl)piperidyl]-1-[(4-chlorophenyl)methyl]-2-oxoethyl)carbamoyl) (3S)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;
- N-((1R)-1-[(4-chlorophenyl)methyl]-2-[4-(2-[(2-cyanophenyl)sulfonyl]amino)-phenyl)piperidyl]-2-oxoethyl) ((3S) (3-1,2,3,4-
- 10 tetrahydroisoquinolyl))carboxamide;
- N-((1R)-1-[(4-chlorophenyl)methyl]-2-oxo-2-[4-(2-[(2,4,6-trimethylphenyl)sulfonyl]amino)phenyl)piperidyl]ethyl) ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;
- N-((1R)-1-[(4-chlorophenyl)methyl]-2-(4-(2-[(methylamino)carbonylamino]-phenyl)piperidyl)-2-oxoethyl) ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;
- 15 N-((1R)-1-[(4-chlorophenyl)methyl]-2-[4-[2-(methoxycarbonylamino)phenyl]piperidyl]-2-oxoethyl) ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;
- 20 N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-[2-[(cyclopropylmethyl)amino]-phenyl)piperidyl]-2-oxoethyl] ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide;
- 25 N-[(1R)-1-[(4-chlorophenyl)methyl]-2-(4-[2-[(cyclopropylmethyl)amino]-phenyl)piperidyl]-2-oxoethyl] ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide; and
- N-[(1R)-2-(4-{2-[(2-aminoethyl)amino]phenyl)piperidyl}-1-[(4-chlorophenyl)methyl]-2-oxoethyl] ((3S) (3-1,2,3,4-tetrahydroisoquinolyl))carboxamide.
- 30 17. Compound of Claim 12 wherein R¹² is selected from optionally substituted benzyl, and optionally substituted 5-10-membered heteroaryl; and wherein R^{13a} and R^{13b} are independently H or chloro.

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18. Compound of Claim 17 wherein R¹² is selected from oxazolo[5,4-b]pyridin-2-yl, oxazolo[4,5-b]pyridin-2-yl, 4-chlorobenzyl, benzoxazol-2-yl and benzyl.

5 19. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound as in any of Claims 1-18.

10 20. A method of treating obesity in a subject, said method comprising administering an effective amount of a compound of Claims 1-18.

15 21. A method of treating diabetes mellitus in a subject, said method comprising administering an effective amount of a compound of Claims 1-18.

20 22. A method of treating disorders related to activation of a G-protein coupled receptor, in a mammal, said method comprising administering an effective amount of a compound of Claims 1-18.

23. The method of Claim 22 wherein the receptor is a melanocortin receptor.

25 24. The method of Claim 23 wherein the melanocortin receptor is MC4R.

INTERNATIONAL SEARCH REPORT

In onal Application No
PCT/US 02/23616

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/445 C07D211/28 C07K5/078 A61P3/04 C07D401/12
C07D211/34 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 74679 A (PATCHETT ARTHUR A ;PLOEG LEONARDUS H T V D (US); SEBHAT IYASSU (US) 14 December 2000 (2000-12-14) cited in the application examples page 49, line 1 - line 10; claims 1,19-21 -----	1-24
X	US 5 721 251 A (PATCHETT ARTHUR A ET AL) 24 February 1998 (1998-02-24) column 2, line 22 -column 27, line 15 column 48, line 53 -column 49, line 2 -----	1-24
X	WO 98 11128 A (EBERLEIN WOLFGANG ;ENTZEROTH MICHAEL (DE); HALTERMAYER GERHARD (DE) 19 March 1998 (1998-03-19) examples where A = A0 claims 1,9 ----- -/-	1-24

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2002	16/10/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Seymour, L

INTERNATIONAL SEARCH REPORT

Inte
onal Application No
PCT/US 02/23616

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2002/091090 A1 (HAY BRUCE A ET AL) 11 July 2002 (2002-07-11) paragraph '0129!; claim 1; examples 1,8,20,28,29 -----	1-24
E	WO 02 070511 A (RUEDIGER EDWARD H ;RUEL REJEAN (CA); THIBAULT CARL (CA); POINDEXTE) 12 September 2002 (2002-09-12) page 29, line 9 - line 13; claims 1,4,8; table 8 -----	1-24
E	WO 02 059117 A (MANCOSO VINCENT ;MARTINELLI MICHAEL JOHN (US); ROTHHAAR ROGER RYAN) 1 August 2002 (2002-08-01) claims 1-33, examples page 47, line 5 - line 15 -----	1-24

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7,9-24 (all partially)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the structural search has been restricted to compounds according to claim 8, in which R is an ortho-substituted phenyl ring, k is 1 and R2 is -C(O)R8 where R8 is a tetrahydroisoquinoline or azetidine ring.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 02/23616**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 20-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-7,9-24 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

Information on patent family members

In International Application No
PCT/US 02/23616

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0074679	A	14-12-2000	AU 5306800 A EP 1187614 A1 WO 0074679 A1 US 6350760 B1 US 2002137664 A1		28-12-2000 20-03-2002 14-12-2000 26-02-2002 26-09-2002
US 5721251	A	24-02-1998	US 5492920 A AU 1172995 A BG 100555 A BR 9408019 A CA 2175218 A1 CN 1174504 A CZ 9601342 A3 EP 0739204 A1 FI 961951 A HU 74733 A2 JP 10506091 T LV 11525 A LV 11525 B NO 961865 A PL 322706 A1 SK 56296 A3 WO 9513069 A1		20-02-1996 29-05-1995 31-10-1996 26-08-1997 18-05-1995 25-02-1998 11-12-1996 30-10-1996 08-05-1996 28-02-1997 16-06-1998 20-10-1996 20-02-1997 08-07-1996 16-02-1998 05-02-1997 18-05-1995
WO 9811128	A	19-03-1998	DE 19636623 A1 DE 19720011 A1 AU 721035 B2 AU 4119697 A BG 103250 A BR 9712023 A CN 1230196 A CZ 9900823 A3 EE 9900115 A WO 9811128 A1 EP 0927192 A1 HR 970481 A1 JP 2000505100 T NO 991130 A NZ 334543 A PL 331989 A1 SK 29799 A3 TR 9900537 T2 US 6344449 B1 ZA 9708083 A HU 9904501 A2		12-03-1998 19-11-1998 22-06-2000 02-04-1998 31-05-2000 31-08-1999 29-09-1999 16-06-1999 15-10-1999 19-03-1998 07-07-1999 31-08-1998 25-04-2000 05-05-1999 23-06-2000 16-08-1999 13-03-2000 21-07-1999 05-02-2002 17-12-1999 28-04-2000
US 2002091090	A1	11-07-2002	NONE		
WO 02070511	A	12-09-2002	WO 02070511 A1 WO 02069905 A2		12-09-2002 12-09-2002
WO 02059117	A	01-08-2002	WO 02059117 A1 WO 02059108 A1		01-08-2002 01-08-2002